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**14. ABSTRACT**
We hypothesized that occupational exposure to polychlorinated biphenyls (PCBs) reduces dopamine (DA) terminal densities in the basal ganglia. We found, using β-CIT imaging, a significant negative relationship between current serum PCB concentrations and the density of β-CIT binding **only** in women. We also determined that bone lead, measured using XRF fluorescent techniques, is associated with greater decrements in memory, executive function and motor function in women compared to similarly aged men with similar bone lead levels. These latter findings are the first to demonstrate a sexual dimorphism in these behaviors associated with low to moderate bone lead concentrations. We are writing a manuscript describing changes in these behaviors with bone lead and have previously published two manuscripts describing: (i) the effects of PCB exposure on β-CIT and (ii) the half lives of PCB congeners over a 28 year interval.

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## INTRODUCTION

Aging former capacitor workers, previously employed at capacitor manufacturing facilities located approximately fifty miles north of Albany, NY underwent neuropsychological and neurological exams; completed a comprehensive occupational, residential and dietary questionnaire; had blood drawn to measure serum thyroid hormone and PCB concentrations and underwent a non-invasive test to determine bone lead concentrations in Albany, NY. Finally, approximately 40% of the subjects participated in a second portion of the study that used brain β-CIT SPECT imaging to determine whether prior occupational exposure to PCBs reduces the number of basal ganglia DA terminals. Imaging took place at the Institute for Neurodegenerative Disorders in New Haven, CT under the supervision of Dr. Kenneth Marek.

Results, obtained using β-CIT SPECT imaging, demonstrate that women, but not men, showed an inverse relationship between lipid-adjusted total serum PCB concentrations and DA transporter densities in the absence of differences in serum PCB concentrations. These findings are reported in *Neurobiology of Disease* **38**, 219-225, 2010 and are supported by epidemiological data demonstrating increased Parkinson's disease mortality, again only in women (Steenland *et al*., *Epidemiology* **17**, 8-13, 2006).

In addition, archived serum PCB concentrations were determined in a subset of the study population for whom archived samples from the 1970s were available. Data from the current and archived serum samples allowed us a unique opportunity to model PCB half-lives using a time interval of nearly 30 years. These findings are reported in the *Journal of Exposure Science and Environmental Epidemiology,* 10 March 2010; doi:10.1038/jes.2010.3.

In this final progress report we present results from comprehensive statistical analyses of the relationships between serum PCB concentrations and bone lead concentrations on neuropsychological and neurological endpoints. The vast majority of the effects of PCBs were on neurological endpoints related to Parkinson's disease with the greatest changes seen in women. Those results are similar in nature and direction to changes in dopamine transporter densities determined using SPECT imaging, as reported in *Neurobiology of Disease*, **38**, 219-225, 2010, 'Occupational exposure to PCBs reduces striatal dopamine transporter densities only in women: A β-CIT imaging study'.

Surprisingly, given that bone lead concentrations were not elevated beyond levels seen in the general population (14.4-17 μg lead/mg bone), many measures of memory and executive function were statistically and inversely related to bone lead concentrations, with the greatest changes seen in women. These results are the first to examine the relationships between bone lead concentrations and neuropsychological function in both men *and* women.

In summary, following occupational exposure to PCBs and lead, there were significantly greater decrements in both neurological and neuropsychological performance in women, the majority who were post-menopausal—reinforcing our earlier hypothesis that the sex of the individual plays a key role in influencing the actions of these widespread neurotoxicants.

## STUDY INVESTIGATORS

**Albany, NY Based Testing**

**Richard F. Seegal - Wadsworth Center, New York Sate Dept. of Health (NYSDOH):** Principal Investigator

**Edward F. Fitzgerald - University at Albany, School of Public Health:** Epidemiologist

**Lenore J. Gensburg - University at Albany, School of Public Health:** Tracing, Screening, Residential, Occupational, Dietary and Medical Histories

**Eric S. Molho, Donald S. Higgins - Albany Medical Center:** Neurological Assessment

**Stewart A. Factor - Emory University:** Neurological Assessment

**Robert J. McCaffrey - University at Albany:** Neuropsychological Assessment

**Richard F. Haase - University at Albany:** Biostatistician

**Mary S. Wolff - Mount Sinai School of Medicine:** Serum PCB Analyses

**Andrew C. Todd - Mount Sinai School of Medicine:** Bone Lead Determination

**Patrick J. Parsons - Wadsworth Center, NYSDOH:** Bone Lead Determination

**New Haven, CT Based Testing**

**Kenneth Marek, John P. Seibyl, Danna Jennings - Institute for Neurodegenerative Disorders:** ß-CIT SPECT Brain Imaging

## PROGRESS IN FISCAL YEAR 2010

The following narrative details the progress we have made in the ongoing data analysis during the eighth and final year of the project. Data collection ended in April 2006 and in Table I we summarize the final tracing, screening and participation rates. We tested 241 subjects in Albany which represents 97% of our projected goal of testing 248 subjects. In addition, 89 of those subjects traveled to New Haven, CT to undergo β-CIT imaging to estimate the density of basal ganglia dopamine transporters. This number represents 93% of our stated goal of testing 96 subjects.

We have published the two manuscripts listed below and have now completed detailed statistical analysis of the effects of PCBs and bone lead on neuropsychological and neurological function. These data will be used to prepare manuscripts describing the interactions between the occupational neurotoxicants we studied (PCBs and lead) and the sex of the individual.

Seegal RF, Fitzgerald EF, Hills EA, Wolff MS, Haase RF, Todd AC, Parsons P, Molho ES, Higgins DS, Factor SA, Marek KL, Seibyl JP, Jennings DL and McCaffrey RJ**.** Estimating the half-lives of PCB congeners in former capacitor workers measured over a twenty-eight year interval. *Journal of Exposure Science and Environmental Epidemiology*, 10 March 2010; doi:10.1038/jes.2010.3.

Seegal RF, Marek KL, Seibyl JP, Jennings DL, Molho ES, Higgins, DS, Factor SA, Fitzgerald EF, Hills EA, Korrick SA, Wolff MS, Haase RF, Todd AC, Parsons P and McCaffrey, RJ. Occupational exposure to PCBs reduces striatal dopamine transporter densities only in women: A *β*-CIT imaging study. *Neurobiology of Disease* 38, 219-225, 2010.

This final progress report will focus on the effects of occupational exposure to PCBs or lead on neuropsychological and neurological variables. In all statistical comparisons presented in the below tables, the effects of each contaminant (*i.e.,* PCBs or lead) are adjusted for each other. Hence, the reported effects of each toxicant have been statistically controlled for any effects due to exposure to the other toxicant.

We present, for clarity's sake, the effects of each toxicant on neuropsychological and neurological endpoints for both men and women combined, and then present the findings where we stratify for sex, that is present the results of the statistical analyses for men and women separately.

In Table I, below, we again present the results of tracing, screening and participation results for the study.

**Table I.** Tracing, screening and participation outcomes among former capacitor workers from Fort Edward and Hudson Falls, New York (N=2,844).

| | N | % |
|---|---|---|
| **Tracing Outcome** | | |
| Eligible for screening | 1124 | 39.52 |
| Not eligible for screening | | |
| Living | 256 | 9.00 |
| Dead | 844 | 28.68 |
| Unlocatable | 577 | 20.29 |
| End of Study | 43 | 1.51 |
| **Screening Outcome** | | |
| Eligible for participation | 484 | 43.06 |
| Not eligible for screening | | |
| Medically ineligible | 348 | 30.96 |
| Other ineligible | 50 | 4.45 |
| Refused | | |
| After screening interview | 110 | 9.79 |
| Refused screening interview | 42 | 3.74 |
| Passively | 80 | 7.12 |
| End of Study | 10 | 0.89 |
| **Participation Outcomes** | | |
| Participation in Albany, NY Portion of Study[1] | 241 | 49.79 |
| Participation in New Haven, CT Portion of Study[2] | 89 | 36.93 |

[1] Measures collected in Albany included collection of sera for PCB determination at the Mt. Sinai School of Medicine; neurological and neuropsychological variables and determination of bone lead concentrations.
[2] β-CIT SPECT imaging of basal ganglia dopamine transporter densities were determined at the Institute for Neurodegenerative Studies.

We present, as Table A in the Appendix, a list of domains/tests, as well as covariates included in the Final Multivariate Regression Statistical Models that will be presented in the body of the progress report. These tests include an intelligence test (the New Adult Reading Test-Revised); measures of memory and learning, motor function, executive function, reaction time, visuospatial recognition, an olfactory test, measures of affective state (anxiety and depression) and measures of neurological function identical to those used to diagnose individuals with Parkinson's disease. Covariates were included in the statistical analyses if they were statistically related to the endpoint of interest with a $p \leq 0.1$.

Analytical Procedures for the Measurement of Tibial Bone Lead

Because we have previously described the procedures for measurement of serum PCB concentrations, we present for reasons of brevity, the techniques used to determine tibial bone lead concentrations. Tibial bone lead concentrations were assessed at the left mid-tibia shaft *via* a 30-minute measurement using $^{109}$Cd-based K-shell x-ray fluorescence (XRF) method [2,8,9] that has since undergone further repeatability assessment [7] and validation [10]. All point estimates, including negative values, were retained in the statistical analyses in order to minimize bias and avoid censoring of data [1]**.** The radiation dose and consequent risk are very small for all age groups [9]. As in previous studies, plaster-of-Paris calibration standards (surrogate bone) were spiked with known amounts of lead (eight standards, ranging from a nominal blank to 132 μg/g, encompassing the range of *in vivo* environmental and occupational exposure levels encountered) and were used to calibrate the bone lead measurement system. The Kα1 and Kβ1 x-ray peaks were be used to obtain *in vivo* concentration estimates *via* comparison to the calibration line obtained from the calibration standards [4]. Measurement uncertainty [11] was also calculated, according to published algorithms [3,5,6]. Bone lead measurements are expressed as micrograms of lead per gram of bone mineral (μg/g).

Statistical Relationships between Bone Lead or Serum PCB Concentrations and Neuropsychological and Neurological Measures (Men and Women Combined).

In Table II, below, we present findings for the above mentioned neuropsychological and neurological variables for bone lead and for total current serum PCB concentrations. As mentioned above, the statistical relationships between the domains and tests for both PCBs and bone lead have been statistically adjusted for each other. Hence, the statistical relationships between each contaminant and the endpoints of interest are independent of each other. Although the individuals whose tibial bone lead concentrations were measured were employed at capacitor factories, tibial bone lead concentrations averaged between 14.4 and 17.7 μg lead/mg bone—clearly within the range reported for individuals who were not occupationally exposed to lead [12]. Nevertheless, there are **nineteen** endpoints that are statistically associated with bone lead concentrations at a $p \leq 0.1$ the majority being decrements in neuropsychological function. In contrast, only five variables, were associated with serum PCB concentrations.

**Table II.** Final multivariable models[a] for neuropsychological and neurological tests with serum total PCB concentration (ng/g lipid and log transformed) and bone lead concentration (μg/g) (N=230).

| | Bone Lead adjusting for Total PCBs | | | Total PCB adjusting for Bone Lead | | |
|---|---|---|---|---|---|---|
| **Domains and Tests** | **β)** | **SE** | **P-value** | **β** | **SE** | **P- value** |
| **INTELLIGENCE TEST** [b] | | | | | | |
| **New adult reading test-revised** | -0.1385 | 0.0539 | **0.0109** | -0.4609 | 1.5734 | 0.7699 |
| **MEMORY AND LEARNING** [b] | | | | | | |
| California Verbal Learning Test (CVLT), 1-5 trial t-score | -0.0725 | 0.0748 | 0.3337 | 0.6741 | 2.1257 | 0.7515 |
| CVLT, List A trial 1 | -0.0143 | 0.0130 | 0.2735 | -0.0245 | 0.3869 | 0.9495 |
| **CVLT, List A Short Delay Free Recall** | -0.0413 | 0.0192 | **0.0330** | 0.0130 | 0.5482 | 0.9811 |
| CVLT, List A Long Delay Free Recall | -0.0322 | 0.0197 | 0.1037 | 0.0318 | 0.5867 | 0.9568 |
| CVLT, Learning slope | 0.0011 | 0.0050 | 0.8266 | -0.0340 | 0.1360 | 0.8026 |
| CVLT, Proactive Interference (List B Compared to List A trial 1) | 0.0970 | 0.2156 | 0.6532 | 6.1177 | 5.7602 | 0.2894 |
| **Wechsler Memory Scale (WMS), Logical Memory Immediate Recall** | -0.0877 | 0.0358 | **0.0150** | -0.2042 | 1.0578 | 0.8471 |
| **WMS, Logical Memory Delayed Recall** | -0.0821 | 0.0351 | **0.0202** | -0.4627 | 1.0292 | 0.6535 |
| WMS, Visual Reproduction Immediate Recall | -0.0201 | 0.0194 | 0.3017 | -0.1871 | 0.5754 | 0.7454 |
| **WMS, Visual Reproduction Delayed Recall** | -0.0490 | 0.0225 | **0.0303** | -0.2429 | 0.6611 | 0.7136 |
| **MOTOR FUNCTION** | | | | | | |
| Finger Tapping (Dominant Hand)[b] | -0.0808 | 0.0527 | 0.1265 | -1.7553 | 1.5708 | 0.2651 |
| **Finger Tapping (Non-Dominant Hand)[b]** | -0.0983 | 0.0448 | **0.0293** | 0.1023 | 1.3108 | 0.9379 |
| Grooved Pegboard (Dominant Hand)[c] | -0.0003 | 0.0006 | 0.6759 | 0.0187 | 0.0182 | 0.3053 |
| Grooved Pegboard (Dominant Hand, Drops)[c] | -0.0096 | 0.0080 | 0.2302 | 0.1893 | 0.1978 | 0.3386 |
| **Grooved Pegboard (Non-Dominant Hand)[c]** | 0.0014 | 0.0007 | **0.0532** | 0.0142 | 0.0200 | 0.4773 |
| **Grooved Pegboard (Non-Dominant Hand, Drops)[c]** | -0.0040 | 0.0096 | 0.6733 | 0.4259 | 0.2216 | **0.0546** |
| Static Motor Steadiness Test (SMST), #2 (Dominant Hand)[c] | 0.0012 | 0.0146 | 0.9368 | -0.5407 | 0.4738 | 0.2539 |
| SMST, #6 (Dominant Hand)[c] | 0.0100 | 0.0106 | 0.3491 | -0.1716 | 0.2949 | 0.5613 |
| SMST, #6 (Dominant Hand, Contacts)[c] | 0.0081 | 0.0108 | 0.4562 | -0.0855 | 0.2934 | 0.7711 |
| **SMST, #6 (Non-Dominant Hand)[c]** | 0.0216 | 0.0089 | **0.0165** | -0.2074 | 0.2593 | 0.4247 |
| **SMST, #6 (Non-Dominant Hand, Contacts)[c]** | 0.0209 | 0.0082 | **0.0114** | 0.1834 | 0.2228 | 0.4114 |
| **EXECUTIVE FUNCTION** | | | | | | |
| **Trail Making Part A, Time To Complete[c]** | 0.0041 | 0.0020 | **0.0427** | 0.0784 | 0.0566 | 0.1675 |
| **Trail Making Part A, Errors[c]** | 0.0249 | 0.0151 | **0.0992** | 0.2386 | 0.3510 | 0.4965 |
| **Trail Making Part B, Time to Complete[c]** | 0.0054 | 0.0025 | **0.0333** | 0.0503 | 0.0715 | 0.4827 |
| **Trail Making Part B, Errors[c]** | 0.0168 | 0.0084 | **0.0468** | 0.2878 | 0.2620 | 0.2720 |
| Stroop Word Test, Raw Score[b] | -0.1448 | 0.1151 | 0.2098 | 1.1000 | 3.4499 | 0.7502 |
| Stroop Color Test, Raw Score[b] | -0.0459 | 0.0875 | 0.6007 | -1.4619 | 2.6238 | 0.5781 |
| Stroop Color-Word Test, Raw Score[b] | -0.0759 | 0.0619 | 0.2220 | -2.1204 | 1.8063 | 0.2419 |

| | Bone Lead adjusting for Total PCBs | | | Total PCB adjusting for Bone Lead | | |
|---|---|---|---|---|---|---|
| **Domains and Tests** | **β)** | **SE** | **P-value** | **β** | **SE** | **P- value** |
| Stroop Interference, Predicted Score[c] | -0.0601 | 0.0449 | 0.1821 | -0.5430 | 1.3072 | 0.6783 |
| Stroop Interference Score[b] | -0.0695 | 0.0541 | 0.2006 | -1.1565 | 1.5779 | 0.4644 |
| **Wisconsin Card Sorting Test (WCST), No. of Trials[c]** | 0.0021 | 0.0012 | **0.0737** | 0.0136 | 0.0323 | 0.6734 |
| **WCST, No. of Correct Responses[b]** | -0.0021 | 0.0013 | 0.1178 | -0.0651 | 0.0349 | **0.0618** |
| **WCST, No. of Errors[c]** | 0.0077 | 0.0037 | **0.0366** | 0.1116 | 0.1109 | 0.3146 |
| **WCST, Percentage of Conceptual Responses[b]** | -0.2904 | 0.1377 | **0.0361** | -6.3682 | 4.0183 | 0.1145 |
| **WCST, No. of Categories Completed[b]** | -0.0057 | 0.0025 | **0.0235** | -0.1249 | 0.0780 | 0.1090 |
| WCST, Learning to Learn[b] | 0.0281 | 0.0623 | 0.6530 | -0.6119 | 1.7489 | 0.7268 |
| **REACTION TIME [c]** | | | | | | |
| **Mean Reaction Time, Dominant Hand** | 0.0049 | 0.0016 | **0.0031** | -0.0241 | 0.0473 | 0.6100 |
| Reaction Time on Hits | 0.0004 | 0.0012 | 0.7546 | -0.0041 | 0.0353 | 0.9087 |
| **Number of False Alarms** | 0.0005 | 0.0100 | 0.9626 | -0.7801 | 0.3269 | **0.0170** |
| **VISUOSPATIAL RECOGNITION [b]** | | | | | | |
| Digit Symbol Coding, Total Correct | -0.0417 | 0.0673 | 0.5360 | -1.4185 | 2.0266 | 0.4847 |
| **Block Design, Total Score** | -0.1550 | 0.0591 | **0.0094** | 0.5307 | 1.7536 | 0.7625 |
| **OLFACTORY TEST [b]** | | | | | | |
| University of Pennsylvania Smell Identification Test | -0.0575 | 0.0373 | 0.1250 | -0.0441 | 1.1265 | 0.9688 |
| **AFFECTIVE STAGE [c]** | | | | | | |
| Anxiety inventory, State Anxiety Raw Score | 0.0020 | 0.0015 | 0.1820 | 0.0634 | 0.0413 | 0.1259 |
| Anxiety inventory, Trait Anxiety Raw Score | -0.0005 | 0.0013 | 0.7007 | -0.0163 | 0.0368 | 0.6578 |
| Beck Depression Inventory, Total Score | -0.0019 | 0.0020 | 0.3548 | -0.0257 | 0.0556 | 0.6444 |
| **NEUROLOGICAL TESTS [c]** | | | | | | |
| Walk Test | -0.0019 | 0.0019 | 0.3309 | 0.0489 | 0.0535 | 0.3604 |
| **Unified Parkinson's Disease Rating Scale** | -0.0001 | 0.0068 | 0.9853 | 0.3815 | 0.1879 | **0.0423** |
| Bradykinesia | 0.0042 | 0.0099 | 0.6753 | 0.1595 | 0.2717 | 0.5572 |
| Tremor | -0.0102 | 0.0089 | 0.2511 | -0.0546 | 0.2383 | 0.8188 |
| **Gait and Posture** | 0.0128 | 0.0093 | 0.1701 | 0.6063 | 0.1377 | **<.0001** |
| Hoehn and Yahr Scale Test | -0.0067 | 0.0207 | 0.7477 | 0.0396 | 0.5502 | 0.9427 |

[a] Adjusted for Variables in Table A (Appendix), [b] Low Score= Impairment, [C] High Score=Impairment
BDI= Beck Depression Inventory, Log Transformed; BMI= Body Mass Index; SE= Standard Error;
Italicized font indicates that either model did not converge or the relative hessian convergence criterion is greater than the limit of 0.0001.
P values ≤ 0.10 are in bold.
Values of Lead are missing (N=11)

Although the results in the above table were statistically adjusted for each contaminant, we chose to further determine, whether there was any evidence for statistical interactions between these two contaminants on tests of neuropsychological and neurological function. In Table III presented below, we show that, except for two variables (both associated with Trail Making Part B), there was no evidence that PCBs and bone lead interacted to alter these tests. This lack of interaction may be due to the fact that, based on Industrial Hygienist Ratings, very few of the capacitor workers had jobs that would have exposed them to both PCBs and lead.

**Table III.** Final multivariable models[a] for neuropsychological and neurological tests with serum total PCB concentration (ng/g lipid and log transformed)—PCB x lead interaction (N= 230).

| Domains and Tests | PCB x Lead | |
|---|---|---|
| | β Interaction | P value |
| **INTELLIGENCE TEST** [b] | | |
| New adult reading test-revised | 4.1370 | 0.1748 |
| **MEMORY AND LEARNING** [b] | | |
| California Verbal Learning Test (CVLT), 1-5 trial t-score | 1.0667 | 0.7921 |
| CVLT, List A trial 1 | -0.0984 | 0.8876 |
| CVLT, List A Short Delay Free Recall | 0.9827 | 0.3264 |
| CVLT, List A Long Delay Free Recall | 0.6430 | 0.5427 |
| CVLT, Learning slope | -0.1351 | 0.6205 |
| CVLT, Proactive Interference (List B Compared to List A trial 1) | 5.8863 | 0.6011 |
| Wechsler Memory Scale (WMS), Logical Memory Immediate Recall | 2.8873 | 0.1385 |
| WMS, Logical Memory Delayed Recall | 1.1057 | 0.5610 |
| WMS, Visual Reproduction Immediate Recall | -0.0589 | 0.9554 |
| WMS, Visual Reproduction Delayed Recall | -0.2073 | 0.8662 |
| **MOTOR FUNCTION** | | |
| Finger Tapping (Dominant Hand)[b] | -1.0287 | 0.7159 |
| Finger Tapping (Non-Dominant Hand)[b] | 0.4260 | 0.8627 |
| Grooved Pegboard (Dominant Hand)[c] | -0.0159 | 0.6238 |
| Grooved Pegboard (Dominant Hand, Drops)[c] | -0.2038 | 0.5978 |
| Grooved Pegboard (Non-Dominant Hand)[c] | 0.0127 | 0.7306 |
| *Grooved Pegboard (Non-Dominant Hand, Drops)*[c] | *-0.6356* | *0.1599* |
| *Static Motor Steadiness Test (SMST), #2 (Dominant Hand)*[c] | -0.6297 | 0.4715 |
| SMST, #6 (Dominant Hand)[c] | 0.6783 | 0.2452 |
| SMST, #6 (Dominant Hand, Contacts)[c] | 0.7820 | 0.1811 |
| SMST, #6 (Non-Dominant Hand)[c] | 0.1868 | 0.7031 |
| SMST, #6 (Non-Dominant Hand, Contacts)[c] | -0.1220 | 0.7824 |
| **EXECUTIVE FUNCTION** | | |
| Trail Making Part A, Time To Complete[c] | -0.0054 | 0.9603 |
| *Trail Making Part A, Errors*[c] | . | . |
| **Trail Making Part B, Time to Complete**[c] | 0.2404 | **0.0725** |

| Domains and Tests | PCB x Lead | |
|---|---|---|
| | β Interaction | P value |
| ***Trail Making Part B, Errors*** [c] | *1.0225* | ***0.0417*** |
| Stroop Word Test, Raw Score [b] | -2.4515 | 0.6826 |
| Stroop Color Test, Raw Score [b] | 0.1998 | 0.9657 |
| Stroop Color-Word Test, Raw Score [b] | 5.2926 | 0.1057 |
| Stroop Interference, Predicted Score [c] | 0.3822 | 0.8737 |
| Stroop Interference Score [b] | 3.8703 | 0.1836 |
| Wisconsin Card Sorting Test (WCST), No. of Trials [c] | -0.0736 | 0.2221 |
| WCST, No. of Correct Responses [b] | 0.0475 | 0.4915 |
| WCST, No. of Errors [c] | -0.3227 | 0.1014 |
| WCST, Percentage of Conceptual Responses [b] | 10.1870 | 0.1603 |
| WCST, No. of Categories Completed [b] | 0.1908 | 0.1624 |
| WCST, Learning to Learn [b] | -1.9111 | 0.5484 |
| **REACTION TIME** [c] | | |
| Mean Reaction Time, Dominant Hand | -0.0543 | 0.5565 |
| Reaction Time on Hits | -0.0013 | 0.9847 |
| *Number of False Alarms* | 0.2481 | 0.6944 |
| **VISUAL AND SPATIAL RECOGNITION** [b] | | |
| Digit Symbol Coding, Total Correct | -1.8646 | 0.6043 |
| Block Design, Total Score | 3.5094 | 0.2685 |
| **OLFACTORY FUNCTION** [b] | | |
| University of Pennsylvania Smell Identification Test | 2.7059 | 0.1735 |
| **AFFECTIVE STAGE** [c] | | |
| Anxiety inventory, State Anxiety Raw Score | 0.0728 | 0.3800 |
| Anxiety inventory, Trait Anxiety Raw Score | -0.0727 | 0.2733 |
| Beck Depression Inventory, Total Score | -0.0572 | 0.5953 |
| **NEUROLOGICAL TESTS** [c] | | |
| Walk Test | 0.0836 | 0.3987 |
| Unified Parkinson's Disease Rating Scale | 0.1401 | 0.6989 |
| Bradykinesia | -0.5643 | 0.2740 |
| Tremor | 0.5430 | 0.2480 |
| Gait and Posture | -0.0549 | 0.8877 |
| Hoehn and Yahr Scale Test | -0.4010 | 0.7206 |

[a] Adjusted for Variables in Table A (Appendix), [b] Low Score= Impairment , [C] High Score=Impairment
BDI= Beck Depression Inventory, Log Transformed; BMI= Body Mass Index; SE= Standard Error;
Italicized font indicates that either model did not converge or the relative hessian convergence criterion is greater than the limit of 0.0001.
P values ≤ 0.10 are in bold.
Values of Lead are missing (N=11)

Statistical Relationships Between Bone Lead or Serum PCB Concentrations and Neuropsychological and Neurological Endpoints for Men and Women

In Table IV, we present the statistical relationships between either bone lead concentrations or total serum PCB concentrations and neuropsychological and neurological endpoints analyzed separately for each sex. There are surprising differences in the relationships between bone lead and these endpoints based on the sex of the worker: seven variables were significantly associated ($p \leq 0.1$) with bone lead concentrations for men (only one for neurological function [Gait and Posture]) while thirteen variables were significantly associated with bone lead concentrations for women (two of the variables were neurological in nature [Tremor, and Gait and Posture]).

The statistical relationships between total serum PCB concentrations and neuropsychological and neurological variables, presented separately for men and women, resulted in fewer significant relationships. For men, only three variables were significant ($p \leq 0.1$), with two of them neurological in nature (The Walk Test and Gait and Posture). For women, five of the endpoints were significantly associated with total serum PCB concentrations—two neuropsychological variables and three neurological variables (Unified Parkinson's Disease Rating Scale, Bradykinesia, and Gait and Posture). As mentioned in the Introduction of this report, the greater significance of the relationships between serum total PCB concentrations and neurological variables in women, are similar to the reductions in β-CIT SPECT imaging we reported last year in the journal Neurobiology of Disease.

**Table IV (Men).** Final multivariable models[a] for neuropsychological and neurological tests with serum total PCB concentration (ng/g lipid and log transformed) and bone lead concentration (ug/g) stratified by sex (N=129).

| Domains and Tests | Men | | | | | |
|---|---|---|---|---|---|---|
| | Lead | | | Total PCB | | |
| | β | SE | P value | β | SE | P value |
| **INTELLIGENCE TEST** [b] | | | | | | |
| **New adult reading test-revised** | -0.1694 | 0.0864 | **0.0531** | -2.6962 | 2.2685 | 0.2377 |
| **MEMORY AND LEARNING** [b] | | | | | | |
| California Verbal Learning Test (CVLT), 1-5 trial t-score | -0.0471 | 0.1090 | 0.6664 | 0.3181 | 2.6216 | 0.9036 |
| CVLT, List A trial 1 | 0.0037 | 0.0202 | 0.8547 | 0.4128 | 0.4447 | 0.3555 |
| CVLT, List A Short Delay Free Recall | -0.0361 | 0.0344 | 0.2964 | -0.2383 | 0.7478 | 0.7506 |
| CVLT, List A Long Delay Free Recall | -0.0253 | 0.0345 | 0.4639 | -0.1955 | 0.7572 | 0.7967 |
| CVLT, Learning slope | -0.0054 | 0.0080 | 0.5034 | -0.2425 | 0.1985 | 0.2249 |
| CVLT, Proactive Interference (List B Compared to List A trial 1) | -0.2307 | 0.3406 | 0.4995 | 5.3577 | 8.5537 | 0.5324 |
| Wechsler Memory Scale (WMS), Logical Memory Immediate Recall | -0.0747 | 0.0666 | 0.2645 | 0.5108 | 1.5347 | 0.7399 |
| **WMS, Logical Memory Delayed Recall** | -0.1769 | 0.0653 | **0.0079** | -0.0534 | 1.4313 | 0.9703 |
| WMS, Visual Reproduction Immediate Recall | -0.0253 | 0.0357 | 0.4796 | -0.2450 | 0.7892 | 0.7569 |
| WMS, Visual Reproduction Delayed Recall | -0.0348 | 0.0431 | 0.4215 | -0.4512 | 0.9603 | 0.6394 |
| **MOTOR FUNCTION** | | | | | | |
| Finger Tapping (Dominant Hand)[b] | -0.1252 | 0.0941 | 0.1860 | -2.2771 | 2.0747 | 0.2748 |
| Finger Tapping (Non-Dominant Hand)[b] | -0.0085 | 0.0796 | 0.9150 | -0.7086 | 1.8270 | 0.6990 |
| Grooved Pegboard (Dominant Hand)[c] | -0.0013 | 0.0011 | 0.2425 | 0.0271 | 0.0235 | 0.2522 |
| Grooved Pegboard (Dominant Hand, Drops)[c] | -0.0108 | 0.0114 | 0.3426 | 0.0823 | 0.2803 | 0.7690 |
| Grooved Pegboard (Non-Dominant Hand)[c] | 0.0007 | 0.0011 | 0.5157 | 0.0198 | 0.0241 | 0.4139 |
| *Grooved Pegboard (Non-Dominant Hand, Drops)*[c] | 0.0068 | 0.0121 | 0.5707 | 0.1906 | 0.2734 | 0.4858 |
| ***Static Motor Steadiness Test (SMST), #2 (Dominant Hand)***[c] | *-0.0380* | *0.0222* | ***0.0867*** | *-0.3209* | *0.5207* | *0.5376* |
| SMST, #6 (Dominant Hand)[c] | 0.0083 | 0.0165 | 0.6154 | 0.1146 | 0.4026 | 0.7764 |
| SMST, #6 (Dominant Hand, Contacts)[c] | -0.0040 | 0.0156 | 0.7991 | 0.2910 | 0.3679 | 0.4308 |
| **SMST, #6 (Non-Dominant Hand)**[c] | 0.0329 | 0.0162 | **0.0442** | -0.0385 | 0.3668 | 0.9167 |
| **SMST, #6 (Non-Dominant Hand, Contacts)**[c] | 0.0271 | 0.0124 | **0.0308** | 0.4193 | 0.2911 | 0.1524 |
| **EXECUTIVE FUNCTION** | | | | | | |
| Trail Making Part A, Time To Complete[c] | 0.0031 | 0.0034 | 0.3528 | 0.0201 | 0.0737 | 0.7857 |
| *Trail Making Part A, Errors*[c] | 0.0201 | 0.0247 | 0.4162 | 0.3253 | 0.4430 | 0.4629 |
| Trail Making Part B, Time to Complete[c] | 0.0052 | 0.0043 | 0.2245 | 0.0355 | 0.0895 | 0.6928 |
| ***Trail Making Part B, Errors***[c] | 0.0151 | 0.0122 | 0.2155 | 0.5360 | 0.3028 | **0.0768** |
| Stroop Word Test, Raw Score[b] | -0.1459 | 0.2103 | 0.4895 | -0.5019 | 4.8681 | 0.9181 |
| Stroop Color Test, Raw Score[b] | 0.0479 | 0.1422 | 0.7371 | -2.9465 | 3.1956 | 0.3590 |
| Stroop Color-Word Test, Raw Score[b] | 0.0511 | 0.1000 | 0.6107 | -3.4249 | 2.2504 | 0.1316 |

| Domains and Tests | Men | | | | | |
|---|---|---|---|---|---|---|
| | Lead | | | Total PCB | | |
| | β | SE | P value | β | SE | P value |
| Stroop Interference, Predicted Score[c] | -0.0519 | 0.0691 | 0.4550 | -1.2233 | 1.7708 | 0.4915 |
| Stroop Interference Score[b] | -0.0703 | 0.0793 | 0.3773 | -1.6341 | 1.8462 | 0.3782 |
| **Wisconsin Card Sorting Test (WCST), No. of Trials[c]** | 0.0048 | 0.0021 | **0.0243** | 0.0518 | 0.0454 | 0.2535 |
| WCST, No. of Correct Responses[b] | 0.0004 | 0.0022 | 0.8554 | -0.0702 | 0.0496 | 0.1568 |
| WCST, No. of Errors[c] | 0.0100 | 0.0068 | 0.1441 | 0.2288 | 0.1529 | 0.1345 |
| WCST, Percentage of Conceptual Responses[b] | -0.2338 | 0.2486 | 0.3492 | -7.3494 | 5.2889 | 0.1676 |
| WCST, No. of Categories Completed[b] | -0.0043 | 0.0044 | 0.3253 | -0.0607 | 0.0985 | 0.5375 |
| WCST, Learning to Learn[b] | 0.0885 | 0.1041 | 0.3981 | -1.0270 | 2.1814 | 0.6390 |
| **REACTION TIME** [c] | | | | | | |
| Mean Reaction Time, Dominant Hand | 0.0037 | 0.0028 | 0.1909 | -0.0322 | 0.0723 | 0.6578 |
| Reaction Time on Hits | -0.0017 | 0.0023 | 0.4582 | 0.0009 | 0.0504 | 0.9853 |
| *Number of False Alarms* | *-0.0004* | *0.0188* | *0.9813* | *-0.4215* | *0.3922* | *0.2826* |
| **VISUOSPATIAL RECOGNITION** [b] | | | | | | |
| Digit Symbol Coding, Total Correct | -0.0317 | 0.1119 | 0.7779 | -0.7650 | 2.4906 | 0.7593 |
| Block Design, Total Score | -0.1605 | 0.1077 | 0.1391 | -0.6740 | 2.3477 | 0.7746 |
| **OLFACTORY TEST** [b] | | | | | | |
| University of Pennsylvania Smell Identification Test | -0.0596 | 0.0750 | 0.4280 | -0.1088 | 1.6641 | 0.9480 |
| **AFFECTIVE STAGE** [c] | | | | | | |
| Anxiety inventory, State Anxiety Raw Score | 0.0012 | 0.0022 | 0.5971 | 0.0832 | 0.0511 | 0.1066 |
| Anxiety inventory, Trait Anxiety Raw Score | -0.0013 | 0.0022 | 0.5631 | -0.0495 | 0.0551 | 0.3710 |
| Beck Depression Inventory, Total Score | 0.0012 | 0.0031 | 0.7084 | 0.0510 | 0.0744 | 0.4947 |
| **NEUROLOGICAL TESTS** [c] | | | | | | |
| **Walk Test** | -0.0008 | 0.0026 | 0.7516 | 0.1421 | 0.0610 | **0.0199** |
| Unified Parkinson's Disease Rating Scale | 0.0166 | 0.0105 | 0.1144 | 0.0289 | 0.2362 | 0.9026 |
| Bradykinesia | 0.0123 | 0.0174 | 0.4797 | -0.2560 | 0.4010 | 0.5233 |
| Tremor | -0.0010 | 0.0116 | 0.9281 | -0.1073 | 0.2746 | 0.6959 |
| ***Gait and Posture*** | *0.0373* | *0.0078* | ***<.0001*** | *0.6912* | *0.3779* | ***0.0674*** |
| *Hoehn and Yahr Scale Test* | *-0.0027* | *0.0271* | *0.9207* | *-0.6279* | *0.7681* | *0.4137* |

[a] Adjusted for Variables in Table A (Appendix), [b] Low Score= Impairment, [C] High Score=Impairment
BDI= Beck Depression Inventory, Log Transformed; BMI= Body Mass Index; SE= Standard Error;
Italicized font indicates that either model did not converge or the relative hessian convergence criterion is greater than the limit of 0.0001.
P values ≤ 0.10 are in bold.
Values of Lead are missing (N=11, men and women combined)

**Table IV (Women).** Final multivariable models[a] for neuropsychological and neurological tests with serum total PCB concentration (ng/g lipid and log transformed) and bone lead concentration (ug/g) stratified by sex (N=112).

| Domains and Tests | Women | | | | | |
|---|---|---|---|---|---|---|
| | Lead | | | Total PCB | | |
| | β | SE | P value | β | SE | P value |
| **INTELLIGENCE TEST** [b] | | | | | | |
| New adult reading test-revised | -0.0988 | 0.0716 | 0.1706 | 1.6360 | 2.3255 | 0.4835 |
| **MEMORY AND LEARNING** [b] | | | | | | |
| California Verbal Learning Test (CVLT), 1-5 trial t-score | -0.0735 | 0.1065 | 0.4913 | 0.8964 | 3.5273 | 0.7999 |
| CVLT, List A trial 1 | -0.0143 | 0.0184 | 0.4413 | -0.7538 | 0.6790 | 0.2697 |
| **CVLT, List A Short Delay Free Recall** | -0.0430 | 0.0247 | **0.0849** | 0.3692 | 0.8353 | 0.6595 |
| CVLT, List A Long Delay Free Recall | -0.0291 | 0.0256 | 0.2571 | 0.4079 | 0.9414 | 0.6658 |
| CVLT, Learning slope | 0.0066 | 0.0063 | 0.2924 | 0.2368 | 0.1917 | 0.2197 |
| CVLT, Proactive Interference (List B Compared to List A trial 1) | 0.3184 | 0.2729 | 0.2462 | 4.5962 | 8.2768 | 0.5800 |
| **Wechsler Memory Scale (WMS), Logical Memory Immediate Recall** | -0.0784 | 0.0448 | **0.0831** | -0.3687 | 1.6787 | 0.8266 |
| WMS, Logical Memory Delayed Recall | -0.0281 | 0.0440 | 0.5248 | -0.2679 | 1.6470 | 0.8711 |
| WMS, Visual Reproduction Immediate Recall | -0.0052 | 0.0252 | 0.8382 | -0.0816 | 0.9365 | 0.9307 |
| WMS, Visual Reproduction Delayed Recall | -0.0405 | 0.0270 | 0.1366 | -0.1572 | 1.0020 | 0.8756 |
| **MOTOR FUNCTION** | | | | | | |
| Finger Tapping (Dominant Hand)[b] | -0.0953 | 0.0660 | 0.1521 | -0.5874 | 2.4295 | 0.8094 |
| **Finger Tapping (Non-Dominant Hand)[b]** | -0.1529 | 0.0559 | **0.0075** | 0.9495 | 1.9380 | 0.6253 |
| Grooved Pegboard (Dominant Hand)[c] | 0.0006 | 0.0008 | 0.4804 | 0.0055 | 0.0292 | 0.8504 |
| Grooved Pegboard (Dominant Hand, Drops)[c] | -0.0034 | 0.0126 | 0.7892 | 0.3930 | 0.3188 | 0.2177 |
| **Grooved Pegboard (Non-Dominant Hand)[c]** | 0.0019 | 0.0010 | **0.0476** | 0.0070 | 0.0337 | 0.8354 |
| *Grooved Pegboard (Non-Dominant Hand, Drops)[c]* | *-0.0074* | *0.0127* | *0.5565* | *0.5531* | *0.4123* | *0.1798* |
| *Static Motor Steadiness Test (SMST), #2 (Dominant Hand)[c]* | 0.0306 | 0.0202 | 0.1306 | -0.7042 | 0.8463 | 0.4054 |
| SMST, #6 (Dominant Hand)[c] | 0.0109 | 0.0142 | 0.4457 | -0.6845 | 0.4488 | 0.1303 |
| SMST, #6 (Dominant Hand, Contacts)[c] | 0.0165 | 0.0151 | 0.2772 | -0.6775 | 0.4723 | 0.1545 |
| SMST, #6 (Non-Dominant Hand)[c] | 0.0159 | 0.0112 | 0.1561 | -0.5727 | 0.3988 | 0.1542 |
| SMST, #6 (Non-Dominant Hand, Contacts)[c] | 0.0151 | 0.0111 | 0.1748 | -0.1535 | 0.3467 | 0.6590 |
| **EXECUTIVE FUNCTION** | | | | | | |
| **Trail Making Part A, Time To Complete[c]** | 0.0051 | 0.0028 | **0.0671** | 0.1530 | 0.0974 | 0.1195 |
| *Trail Making Part A, Errors[c]* | *0.0411* | *0.0000* | . | *0.0381* | *0.0000* | . |
| Trail Making Part B, Time to Complete[c] | 0.0038 | 0.0034 | 0.2580 | 0.0092 | 0.1248 | 0.9413 |
| *Trail Making Part B, Errors[c]* | *0.0208* | *0.0136* | *0.1266* | *-0.2309* | *0.5626* | *0.6815* |
| Stroop Word Test, Raw Score[b] | -0.1145 | 0.1425 | 0.4238 | 3.7283 | 4.9529 | 0.4535 |
| Stroop Color Test, Raw Score[b] | -0.0834 | 0.1278 | 0.5160 | 0.8953 | 4.4770 | 0.8419 |
| Stroop Color-Word Test, Raw Score[b] | -0.1447 | 0.0872 | 0.1004 | 2.4586 | 3.0522 | 0.4226 |
| Stroop Interference, Predicted Score[c] | -0.0551 | 0.0622 | 0.3783 | 0.2927 | 2.0098 | 0.8846 |

| Domains and Tests | Women | | | | | |
|---|---|---|---|---|---|---|
| | Lead | | | Total PCB | | |
| | β | SE | P value | β | SE | P value |
| Stroop Interference Score[b] | -0.0843 | 0.0804 | 0.2972 | -0.3372 | 2.7317 | 0.9020 |
| WCST, No. of Trials[c] | 0.0011 | 0.0014 | 0.4397 | -0.0400 | 0.0475 | 0.4005 |
| **Wisconsin Card Sorting Test (WCST), No. of Correct Responses[b]** | -0.0042 | 0.0017 | **0.0110** | -0.0779 | 0.0498 | 0.1179 |
| **WCST, No. of Errors[c]** | 0.0079 | 0.0047 | **0.0896** | 0.0337 | 0.1776 | 0.8493 |
| **WCST, Percentage of Conceptual Responses[b]** | -0.3672 | 0.1845 | **0.0494** | -8.0617 | 6.8990 | 0.2455 |
| **WCST, No. of Categories Completed[b]** | -0.0059 | 0.0031 | **0.0545** | -0.2174 | 0.1314 | **0.0981** |
| WCST, Learning to Learn[b] | -0.0208 | 0.0891 | 0.8162 | -1.0194 | 2.8545 | 0.7219 |
| **REACTION TIME** [c] | | | | | | |
| **Mean Reaction Time, Dominant Hand** | 0.0053 | 0.0020 | **0.0105** | -0.0347 | 0.0661 | 0.6011 |
| Reaction Time on Hits | 0.0015 | 0.0015 | 0.3085 | -0.0475 | 0.0539 | 0.3806 |
| ***Number of False Alarms*** | *-0.0005* | *0.0124* | *0.9663* | *-0.8665* | *0.4901* | ***0.0770*** |
| **VISUOSPATIAL RECOGNITION** [b] | | | | | | |
| Digit Symbol Coding, Total Correct | -0.0433 | 0.0905 | 0.6333 | -2.8266 | 3.3596 | 0.4022 |
| **Block Design, Total Score** | -0.1298 | 0.0739 | **0.0822** | 2.2496 | 2.7277 | 0.4115 |
| **OLFACTORY TEST** [b] | | | | | | |
| University of Pennsylvania Smell Identification Test | -0.0504 | 0.0400 | 0.2112 | 0.0019 | 1.4963 | 0.9990 |
| **AFFECTIVE STAGE** [c] | | | | | | |
| Anxiety inventory, State Anxiety Raw Score | 0.0028 | 0.0023 | 0.2106 | 0.0627 | 0.0715 | 0.3826 |
| Anxiety inventory, Trait Anxiety Raw Score | 0.0006 | 0.0017 | 0.7220 | 0.0412 | 0.0516 | 0.4260 |
| Beck Depression Inventory, Total Score | -0.0034 | 0.0027 | 0.2074 | -0.1046 | 0.0827 | 0.2089 |
| **NEUROLOGICAL TESTS** [c] | | | | | | |
| Walk Test | -0.0016 | 0.0027 | 0.5550 | 0.0169 | 0.0843 | 0.8412 |
| **Unified Parkinson's Disease Rating Scale** | -0.0151 | 0.0095 | 0.1127 | 0.9580 | 0.3197 | **0.0027** |
| **Bradykinesia** | -0.0026 | 0.0116 | 0.8227 | 0.6787 | 0.3680 | **0.0651** |
| **Tremor** | -0.0307 | 0.0156 | **0.0485** | 0.5020 | 0.4792 | 0.2949 |
| ***Gait and Posture*** | -0.0242 | 0.0135 | **0.0743** | 0.6543 | 0.1785 | **0.0002** |
| *Hoehn and Yahr Scale Test* | *-0.0129* | *0.0000* | *.* | *0.7570* | *0.0000* | *.* |

[a] Adjusted for Variables in Table A (Appendix), [b] Low Score= Impairment, [C] High Score=Impairment
BDI= Beck Depression Inventory, Log Transformed; BMI= Body Mass Index; SE= Standard Error;
Italicized font indicates that either model did not converge or the relative hessian convergence criterion is greater than the limit of 0.0001.
P values ≤ 0.10 are in bold.
Values of Lead are missing (N=11, men and women combined)

## KEY RESEARCH ACCOMPLISHMENTS

We have published the two manuscripts listed below and have now completed detailed statistical analysis of the effects of PCBs and bone lead on neuropsychological and neurological function. These data will be used to prepare manuscripts describing the interactions between the occupational neurotoxicants we studied (PCBs and lead) and the sex of the individual; as well as the relationship between changes in *β*-CIT and neurological function.

Seegal RF, Fitzgerald EF, Hills EA, Wolff MS, Haase RF, Todd AC, Parsons P, Molho ES, Higgins DS, Factor SA, Marek KL, Seibyl JP, Jennings DL and McCaffrey RJ**.** Estimating the half-lives of PCB congeners in former capacitor workers measured over a twenty-eight year interval. *Journal of Exposure Science and Environmental Epidemiology*, 10 March 2010; doi:10.1038/jes.2010.3.

Seegal RF, Marek KL, Seibyl JP, Jennings DL, Molho ES, Higgins, DS, Factor SA, Fitzgerald EF, Hills EA, Korrick SA, Wolff MS, Haase RF, Todd AC, Parsons P and McCaffrey, RJ. Occupational exposure to PCBs reduces striatal dopamine transporter densities only in women: A *β*-CIT imaging study. *Neurobiology of Disease* 38, 219-225, 2010.

Seegal RF, Fitzgerald EF, Hills EA, Molho ES, Higgins, DS, Factor SA, McCaffrey, RJ, Todd AC, Parsons PJ, Wolff MS, Haase RF, Marek KL, Seibyl JP, Jennings DL, and Korrick SA. Sexually dimorphic neuropsychological responses to bone lead in a cohort of former capacitor workers. *Environmental Health Perspectives*, **in preparation**.

## REPORTABLE OUTCOMES

### Published Manuscripts

**1.** Seegal RF, Fitzgerald EF, Hills EA, Wolff MS, Haase RF, Todd AC, Parsons P, Molho ES, Higgins DS, Factor SA, Marek KL, Seibyl JP, Jennings DL and McCaffrey RJ**.** Estimating the half-lives of PCB congeners in former capacitor workers measured over a 28-year interval. *Journal of Exposure Science and Environmental Epidemiology*, 10 March 2010; doi:10.1038/jes.2010.3.

**2.** Seegal RF, Marek KL, Seibyl JP, Jennings DL, Molho ES, Higgins, DS, Factor SA, Fitzgerald EF, Hills EA, Korrick SA, Wolff MS, Haase RF, Todd AC, Parsons P and McCaffrey, RJ. Occupational exposure to PCBs reduces striatal dopamine transporter densities only in women: A $\beta$-CIT imaging study. *Neurobiology of Disease* 38, 219-225, 2010.

**3.** Invited speaker at the International Symposium on Disturbances of Cerebral Function Induced by Food and Water Contaminants. Presented a talk entitled "Sexually Dimorphic Effects of PCBs: From Development to Neurodegeneration", Valencia, Spain, March 2010.

**4.** Invited lecturer at the 26th International Neurotoxicology Conference: Unifying Mechanisms of Neurological Disorders. Presented a talk entitled "Sexually Dimorphic Effects of PCBs: From Development to Neurodegeneration", Portland, OR, June 2010.

**5.** Invited speaker at Vanderbilt University School of Medicine. Presented a seminar entitled "Sexually Dimorphic Effects of PCBs: From Development to Neurodegeneration", Nashville TN, April 2011.

## CONCLUSIONS

In summary, serum PCB concentrations in this cohort of former capacitor plant workers, determined nearly 30 years after direct occupational exposures ceased, remained substantially elevated relative to serum PCB levels seen in individuals residing in the same communities who did not work at the GE capacitor factories. By comparing serum concentrations in a subgroup of workers from 1976 to 2004 we demonstrated that some of the congeners that were occupational in origin have longer half-lives than previously estimated. In general, the half-lives for light occupational congeners were shorter than those for heavy congeners. We have also shown that half-lives for the occupational congeners were inversely proportional to initial body burdens, which may aid in explaining the significantly longer half-lives we observed in women. The revised half-lives should further aid in understanding the toxicological/epidemiological consequences of exposure to PCBs, as well as identifying prior vectors of exposure to PCBs. Finally, prior occupational exposure remained a significant predictor of current serum PCB concentrations, further supporting a consistent and long-duration trend of increased PCB body burden in this cohort of former capacitor workers.

We hypothesized that occupational exposure to PCBs is associated with a reduction in central dopamine (DA) similar to changes previously seen in PCB exposed adult non-human primates. To test that hypothesis we used [$^{123}$I]$\beta$-CIT SPECT imaging to estimate basal ganglia DA transporter density in former capacitor workers. Women, but not men, showed an inverse relationship between lipid-adjusted total serum PCB concentrations and DA transporter densities in the absence of differences in serum PCB concentrations. These sex differences may reflect age-related reductions in the levels of gonadal hormones since these hormones have been shown experimentally to alter response to DA neurotoxicants. These findings may aid in better understanding the roles that sex and age play in modifying central DA function following exposure, not only to PCBs, but also to other DA neurotoxicants as well as further elucidating the role of gonadal hormones in influencing the initiation and/or progression of neurodegenerative disorders. Finally, the unexpected results of this study emphasize not only the need to consider sex as an important variable in determining the central response(s) to known and suspected neurotoxicants but, also suggest broadening the definition of gene x environment interactions to include sex.

Most importantly, the data presented in Tables II-IV, continue to highlight the sexual dimorphism in response of aging men and women former capacitor workers not only to extraordinarily high levels of PCBs (reported here as total serum PCB concentrations) but also to lead (reported here as μg lead/mg bone), *despite* the fact that the levels of bone lead were not significantly different from those reported in individuals who were *not* exposed to lead in an occupational setting.

We will, in the next several months, publish two additional manuscripts. The first will describe the relationships between tibial bone lead concentrations and neuropsychological endpoints. Although others [12] have reported decrements in neuropsychological function in individuals with similar concentrations of bone lead, to the best of our knowledge, no one has examined whether men and women, with similar tibial bone lead concentrations, show differential changes in these endpoints—as we have done. The second manuscript will determine the relationships between total serum PCB concentrations, as well as the relationships between PCB-induced changes in β-CIT SPECT binding to basal ganglia dopamine transporters and changes in neurological measures associated with Parkinson's disease.

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# APPENDIX

**Table A.** List of covariates included in final multivariable regression models by domain and neuropsychological and neurological tests**.**

| Domain And Tests | Covariates (High Risk Group) |
|---|---|
| **INTELLIGENCE TEST** [b] | |
| New Adult Reading Test-Revised | Sex (Male), Education (< 12 Years), Indirect Solvent Exposure Based on Hobbies (Yes), Occupational Exposure to Pesticides (Yes), BDI(+), Diabetes (Yes) |
| **MEMORY AND LEARNING** [b] | |
| California Verbal Learning Test (CVLT), 1-5 trial t-score | Sex (Male), Education (<12 Years), State Anxiety (+) |
| CVLT, List A trial 1 | Age (+), Sex (Male), Education (< 12 Years), State Anxiety (+) |
| CVLT, List A Short Delay Free Recall | Age (+), Sex (Male), Education (< 12 Years of Education) |
| CVLT, List A Long Delay Free Recall | Age (+), Sex (Male), Education (< 12 Years), State Anxiety (+) |
| CVLT, Learning slope | BDI (+) |
| CVLT, Proactive Interference (List B Compared to List A trial 1) | Direct Solvent Exposure Based on Hobbies, Osteoporosis, Other NSAIDs, Diuretics----- |
| Wechsler Memory Scale (WMS), Logical Memory Immediate Recall | Age(+), Education(<12 Years), No. of Cigarette Packs in the Previous Year (-), Occupational Exposure to Pesticides (Yes), State Anxiety (+) |
| WMS, Logical Memory Delayed Recall | Age (+), Education (<12 Years),No. of Cigarette Packs in the Previous Year (-), Occupational Exposure to Solvents (Yes), State Anxiety (+) |
| WMS, Visual Reproduction Immediate Recall | Age (+), Education (<12 Years), State Anxiety (+), Total no. of Drinks per Week in the Previous Year (+), Sympathomimetic Agent (No) |
| WMS, Visual Reproduction Delayed Recall | Age (+), Education (< 12 Years), State Anxiety (+) |
| **MOTOR FUNCTION** | |
| Finger Tapping (Dominant Hand)[b] | Age (+), Sex (Female), Education (< 12 Years) |
| Finger Tapping (Non-Dominant Hand)[b] | Age (+), Sex (Female), Hypertension (Yes), Diabetes (Yes), BDI (+), Trait Anxiety (+) |
| Grooved Pegboard (Dominant Hand)[c] | Age (+), Sex (Male), Education (< 12 Years), Hypoglycemic Agents (Yes), Diuretics (Yes) |
| Grooved Pegboard (Dominant Hand, Drops)[c] | Hypertension (Yes), Marital Status (Single) |
| Grooved Pegboard (Non-Dominant Hand)[c] | Age (+), Sex (Male), Hypertension (Yes), State Anxiety (+), Diuretics (Yes), Hypoglycemic Agents (Yes) |
| Grooved Pegboard (Non-Dominant Hand, Drops)[c] | Sex (Male), Combined Disease (Yes) |
| Static Motor Steadiness Test (SMST), #2 (Dominant Hand)[c] | Age (+), Total no. of Drinks per Week in the Previous Year (+) |
| SMST, #6 (Dominant Hand)[c] | Beta-adrenergic blocking agent (Yes) |
| SMST, #6 (Dominant Hand, Contacts)[c] | Hypertension (Yes) |
| SMST, #6 (Non-Dominant Hand)[c] | Age (+), Total no. of Drinks per Week in the Previous Year (+),No. of Cigarette Packs in the Previous Year (+) |
| SMST, #6 (Non-Dominant Hand, Contacts)[c] | Sex (Male) |

| **EXECUTIVE FUNCTION** | |
|---|---|
| Trail Making Part A, Time To Complete[c] | Age (+), Hypertension (Yes), Trait Anxiety (+) |
| Trail Making Part A, Errors[c] | Education (Yes), Income (High), Combined Disease (Yes) |
| Trail Making Part B, Time to Complete[c] | Age (+), Education (<12 Years), Hypertension (Yes), Trait Anxiety (+), Other NSAIDs (No) |
| Trail Making Part B, Errors[c] | Muscle and Joint Conditions (Yes) |
| Stroop Word Test, Raw Score[b] | Age (+), Sex (Male), Education (<12 Years), State Anxiety (+), Diuretics (Yes) |
| Stroop Color Test, Raw Score[b] | Age (+), Sex (Male), Education (<12 Years), State Anxiety (+), Marital Status (Yes), Beta-adrenergic blocking agent (Yes) |
| Stroop Color-Word Test, Raw Score[b] | Age (+), Education (<12 Years), State Anxiety (+), Beta-adrenergic Blocking Agent(+) |
| Stroop Interference, Predicted Score[c] | Sex, Education, State Anxiety, Beta-adrenergic Blocking Agent, Diuretics, Marital Status |
| Stroop Interference Score[b] | Age, Sex, Arthritis |
| Wisconsin Card Sorting Test (WCST), No. of Trials[c] | Age (+), Other NSAIDs (No), Psychotherapeutic Agents (Yes) |
| WCST, No. of Correct Responses[b] | Education (<12 Years), No. of Cigarette Packs in the Previous Year (+), Electrolytic Replacements (Yes) |
| WCST, No. of Errors[c] | Age (+), Education (<12 Years), State Anxiety (+), Other NSAIDs (No) |
| WCST, Percentage of Conceptual Responses[b] | Age (+), Education (< 12 Years), State Anxiety (+), Other NSAIDs (No) |
| WCST, No. of Categories Completed[b] | Age (+), Education (<12 Years), State Anxiety (+), Muscle and Joint Conditions (Yes), Other NSAIDs (No) |
| WCST, Learning to Learn[b] | Age (+), Sex (Female), Education (<12 Years), Direct Exposure to Solvents Based on Hobbies (Yes), Muscle and Joint Conditions (Yes), Psychotherapeutic Agents (Yes) |
| **REACTION TIME** [c] | |
| Mean Reaction Time, Dominant Hand | Other NSAIDs (No), Psychotherapeutic Agents (Yes), Diuretics (Yes), BDI (+) |
| Reaction Time on Hits | Age (+), Education (<12 Years), Occupational Exposure to Solvents (Yes), Trait Anxiety (+) |
| Number of False Alarms | Age (+), Education (<12 Years) |
| **VISUOSPATIAL RECOGNITION** [b] | |
| Digit Symbol Coding, Total Correct | Age (+), Sex (Male), Education (<12 Years), State Anxiety (+), Marital Status (Yes) |
| Block Design, Total Score | Age, (+) Sex (Female), Education (< 12 Years), Trait Anxiety (+), Diuretics (Yes), Other NSAIDs (No) |
| **OLFACTORY TEST** [b] | |
| University of Pennsylvania Smell Identification Test | Age (+), Sex (Male), Education (<12 Years), State Anxiety (+), Beta-adrenergic Blocking Agent (Yes) |
| **AFFECTIVE STAGE** [c] | |
| Anxiety inventory, State Anxiety Raw Score | Income (Low ), Total no. of Drinks per week in the Last Year (+), Trait Anxiety (+) |
| Anxiety inventory, Trait Anxiety Raw Score | BDI (+), State Anxiety (+) |
| Beck Depression Inventory, Total Score | Sex (Female), Combined Disease (Yes), Muscle and Joint Conditions (Yes), Trait Anxiety (+), Psychotherapeutic Agents (Yes) |
| **NEUROLOGICAL TESTS** [c] | |
| Walk Test | Age (+), Arthritis (Yes), Anticonvulsants (Yes), Psychotherapeutic Agents (Yes), BMI (+) |
| Unified Parkinson's Disease Rating Scale | Income (low), Occupational Exposure to Pesticides (Yes), Hypertension (Yes), State Anxiety (-), COX2 Inhibitors (Yes), Other NSAIDs (No), Anticonvulsants (Yes) |

| | |
|---|---|
| Bradykinesia | Age (+), Hypertension (Yes), COX2 Inhibitors (Yes), Anticonvulsants (Yes) |
| Tremor | Age (+), Sex (Female), State Anxiety (+) |
| Gait and Posture | No. of Cigarette Packs in the Last Year (+) |
| Hoehn and Yahr Scale Test | Hypertension (Yes) |

[a b] Low Score= Impairment
[C] High Score=Impairment
BDI= Beck Depression Inventory, Log Transformed; BMI= Body Mass Index

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'Neurological Effects of Polychlorinated Biphenyls – Does Occupational Exposure Alter Dopamine-Mediated Function?', invited presenter at the New York Academy of Sciences conference titled: "Parkinson's Disease: The Life Cycle of the Dopamine Neuron", Princeton, NJ, September 2002.

'Does Occupational Exposure to Polychlorinated Biphenyls Alter Dopamine-Mediated Neurological Function?', International Neurotoxicology Association (INA9) Meeting, Dresden, Germany, June 2003.

'Biological Bases for PCB Induced Alterations in Dopamine-Mediated Neurological Function', presented at the Twenty-First International Neurotoxicology Conference in Honolulu, HI, February 2004.

'PCBs, Dopamine and Cell-Death–Relevance to Human Exposure', presented at the Superfund Basic Research Program Conference 'Persistent Contaminants: New Priorities, New Concerns' in Bear Mountain, NY, September 2004.

'Biological Bases for PCB Induced Alterations in Dopamine-Mediated Neurological Function', presented at the Annual Meeting of the Society of Toxicology in New Orleans, LA, March 2005.

'Polychlorinated Biphenyls Alter Dopamine Function in Older Capacitor Workers', presented at the invitation of the U.S. Army in a session jointly sponsored by the U.S. Army Research Institute of Environmental Medicine and the U.S. Army Medical Research and Materiel Command entitled 'Neurotoxicant Exposure in Military Deployments and Putative Associations with Neurodegenerative Diseases' at the Twenty-Second International Neurotoxicology Conference in Research Triangle Park, NC, September 2005.

'PCB Exposure and Parkinson's Disease', invited lecture presented in the Toxic Risks with Aging–2005 Spring Symposium at Duke University sponsored by the Duke University Integrated Toxicology Program, Superfund Basic Research Program, Center for the Study of Aging and Human Development, and the National Institute of Environmental Health Science, April 2005.

'PCB-Induced Neurodegeneration: Altered Dopamine Storage and Oxidative Stress', invited seminar at the University of Iowa, Iowa City, IA, March 2006.

'Polychlorinated Biphenyl-Induced Neurotoxicity: Relevance to PD', invited plenary lecture speaker at the annual meeting of the Collaborative Centers for Parkinson's Disease Environmental Research sponsored by The Parkinson's Institute; Asilomar, CA, April 2007.

'Polychlorinated Biphenyl-Induced Neurotoxicity: Relevance to PD', invited seminar speaker at Emory University School of Medicine, Center for Neurodegenerative Disease, Atlanta, GA, April 2007.

Invited participant at the Parkinson's Institute's Scientific Consensus Conference 'Parkinson's Disease and the Environment', Sunnyvale, CA, June 2007.

'The Influence of Gender and Aging on the Effects of Environmental Toxicants in PD', invited speaker in plenary session 'Modifiers of Disease Development in Parkinson's Disease: Role of Environmental Toxicants' 24th International Neurotoxicology Conference, San Antonio, TX, November 2007.

'Polychlorinated Biphenyl Neurotoxicity: Relevance to PD', invited seminar speaker at the Stratton VA Medical Center, Albany, NY, October 2007.

Invited discussion leader for the scientific session: 'Gene-Environment Interaction in Neurodegenerative Disease' at the Gordon Research Conference: Mechanisms of Toxicity; Lewiston, ME, July 2008

'Does Reproductive Senescence Alter Gender Differences in PCB-Induced Changes in Central Dopaminergic Function', presented as an invited participant serving on the Conference Program Committee at the 25th International Neurotoxicology Conference: Environmental Etiologies of Environmental Disorders, Rochester, NY, October 2008.

"Sexually Dimorphic Effects of PCBs: From Development to Neurodegeneration", invited speaker at the International Symposium on Disturbances of Cerebral Function Induced by Food and Water Contaminants, Valencia, Spain, March 2010.

"Sexually Dimorphic Effects of PCBs: From Development to Neurodegeneration" invited lecturer at the 26th International Neurotoxicology Conference: Unifying Mechanisms of Neurological Disorders, Portland, OR, June 2010.

'Sexually Dimorphic Effects of PCBs: From Development to Neurodegeneration'. Invited seminar speaker at Vanderbilt University School of Medicine, Nashville TN, April 2011.

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# Occupational exposure to PCBs reduces striatal dopamine transporter densities only in women: A β-CIT imaging study

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ABSTRACT

We hypothesize that occupational exposure to PCBs is associated with a reduction in central dopamine (DA) similar to changes previously seen in PCB exposed adult non-human primates. To test that hypothesis, we used [$^{123}$I]β-CIT SPECT imaging to estimate basal ganglia DA transporter density in former capacitor workers. Women, but not men, showed an inverse relationship between lipid-adjusted total serum PCB concentrations and DA transporter densities in the absence of differences in serum PCB concentrations. These sex differences may reflect age-related reductions in the levels of gonadal hormones since these hormones have been shown experimentally to alter response to DA neurotoxicants. These findings may aid in better understanding the roles that sex and age play in modifying central DA function following exposure, not only to PCBs, but also to other DA neurotoxicants as well as further elucidating the role of gonadal hormones in influencing the initiation and/or progression of neurodegenerative disorders.



## Introduction

Polychlorinated biphenyls (PCBs) are widely dispersed in the environment due to leakage from electrical transformers and capacitors as well as release from factories that manufactured these components (Erickson, 1997; Horn et al., 1979; National Research Council, 1979). Epidemiological studies show that developmental exposure to foods contaminated by PCBs results in possible cognitive deficits in infants and children (Jacobson and Jacobson, 2003; Stewart et al., 2005).

Negative consequences are also seen in adults. Schantz et al. (2001) and Fitzgerald et al. (2007; 2008) demonstrate, respectively, subtle cognitive and behavioral changes in recreational fishermen from the Great Lakes and in adults who consumed PCB-contaminated fish from the upper Hudson River. In addition, Seegal et al. (1991) demonstrated that adult non-human primates exposed to PCBs, resulting in serum levels at the upper range reported in capacitor workers (Wolff et al., 1982b), significantly reduced basal ganglia dopamine (DA) concentrations—an effect that persisted for months following cessation of exposure (Seegal et al., 1994a).

These findings provide the rationale for studying adults whose occupational exposure to PCBs resulted in serum levels 10- to 20-fold higher than in the general population (Lawton et al., 1985). Furthermore, this population represents one of the most highly exposed in the United States and the majority of the workers were exposed only to PCBs. Thus, this cohort provides the opportunity to determine whether changes in central DA, as seen in adult non-human primates (Seegal et al., 1994a), also occur in occupationally exposed humans.

In this study, we used *in vivo* molecular imaging of the dopamine transporter (DAT) to investigate the effects of occupational exposure to PCBs on striatal DAT density in male and female former capacitor

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workers. This imaging technique has been widely used to assess striatal DAT density in both healthy subjects and in subjects with degenerative disorders characterized by dopaminergic dysfunction, including Parkinson's disease (PD) and diffuse Lewy body disease (Colloby et al., 2005). Importantly, recent studies by Prince et al. (2006) and Steenland et al. (2006) found that women former capacitor workers had significantly higher mortality from PD than did men. The Steenland et al. study (2006) is of particular import because the subjects were from the same cohort we studied.

Because of the known and/or suggested neuroprotective effects of ovarian hormones—i.e., (i) women have a lower incidence of idiopathic PD than do men (Baldereschi et al., 2000; Wenning et al., 2005); (ii) bilateral oophorectomy increases the incidence of PD (Benedetti et al., 2001); (iii) female rodents demonstrate smaller changes in central DA concentrations following exposure to DA neurotoxicants than do comparably exposed male animals (Dluzen, 2000; Miller et al., 1998); and (iv) ovariectomy exacerbates DA loss following exposure to DA neurotoxicants, an effect largely prevented by estrogen supplementation (Dluzen, 2000; Miller et al., 1998)—we included sex as a variable in all statistical analyses. Our original hypothesis is that workers with higher serum PCB concentrations will have lower DAT densities and that the association will be stronger among men than women.

## Methods

### *Study population*

The population consisted of 6798 former men and women capacitor workers who had been employed by General Electric Corporation (GE) at either of two capacitor factories in upstate New York (Ft. Edward and Hudson Falls) for at least 3 months between 1946 and 1977. In 1977, the use of PCBs at these sites was banned by the U.S. Environmental Protection Agency (1978). A complete description of the study population, the tracing and screening procedures, the demographics of the cohort and serum PCB concentrations is presented elsewhere by Seegal et al. (in press).

A total of 241 men and women who lived within a 100 mile radius of Albany, NY participated in the study that included neurological and neuropsychological assessments, determination of bone lead concentrations, circulating thyroid hormone levels and serum PCB concentrations. Eighty-nine of those subjects (50 men and 39 women; 37% of the total study population) agreed to participate in the imaging portion of the study conducted at the Institute for Neurodegenerative Disorders in New Haven, CT. The results of the imaging portion of the study are presented here.

### *Human subject protection*

Prior to initiation of the study, the design and instruments, including those associated with tracing, screening, recruitment, and data collection, were reviewed and approved by Institutional Review Boards at each of the study's collaborating institutions (NYSDOH, Albany Medical Center, University at Albany, Institute for Neurodegenerative Disorders and the U.S. Army).

### *β-CIT imaging techniques*

Subjects underwent [$^{123}$I]β-CIT SPECT imaging as previously described (Laruelle et al., 1994; Seibyl et al., 1995). High specific activity [$^{123}$I]β-CIT was prepared from the corresponding trimethylstannyl precursor and subjects were injected with up to 6 mCi of [$^{123}$I]β-CIT (Innis et al., 1993). Manual regions of interest (ROI) analysis of the [$^{123}$I]β-CIT/SPECT scans was performed using previously described methods (Seibyl et al., 1995), by a nuclear medicine technologist who was blinded to the serum PCB concentration of all participants. The primary quantitative imaging outcome measure, the specific non-displaceable putamen uptake (V3"), was determined through a standardized analysis method (Seibyl et al., 1995).

### *Measurement of serum PCB concentrations*

The method for the analysis of serum PCB concentrations is described elsewhere (Seegal et al., in press). Briefly, the analytical methods of Gammon et al. (2002) and Brock et al. (1996) were followed to determine concentrations of 27 individual PCB congeners and nine organochlorine pesticides. Total serum lipids were determined from serum cholesterol and triglycerides using the algorithm of Phillips et al. (1989).

In addition to measuring total serum PCB concentrations, serum concentrations of 'light', 'heavy' and 'occupational' PCB congeners were also determined. Light was defined as those PCB congeners eluting prior to DDE; heavy as those congeners eluting after DDE (Wolff et al., 1982a) and 'occupational' (Wolff, personal communication) defined as those congeners that were unique markers of occupational exposure—i.e., congeners whose concentrations were low in the general population and were derived from exposure to the Aroclor mixtures used in the capacitor plants. These occupational congeners included (PCB28, PCB74, PCB118, PCB105, and PCB156).

Because the distribution of lipid-adjusted serum PCB concentrations was positively skewed, the data were log-transformed and all statistical analyses used that metric. Graphic examination of the β-CIT variable revealed that it was symmetrically distributed and required no transformation.

### *Statistical procedures*

The statistical analysis proceeded in three stages. First, the direct effects of age and sex on the relationships between PCBs and striatal DAT densities were determined using the univariate general linear model of Draper and Smith (1981). Next, we determined the correlations between log-adjusted serum PCB concentrations, age, sex and other relevant variables (see Table 3) that were associated either with exposure and/or outcome (β-CIT SPECT). In order to control for these potential confounders, we evaluated the correlation of each of them to either PCBs or β-CIT for any variable whose correlation with both exposure and outcome was significant at $p<0.20$. Finally, we evaluated the fitted parameter estimates both with and without potential confounder(s). If inclusion of the confounder resulted in a shift greater than 10% in the estimate for PCBs on β-CIT, it was retained in the final model; otherwise it was dropped from further consideration as a confounder. As discussed in greater detail below, the final statistical model included age, body mass index and sex.

## Results

### *The β-CIT cohort and comparisons with non-participants*

Table 1 summarizes the means and standard deviations of demographic and background characteristics for the 89 individuals who participated in the imaging study, as well as highlighting any significant differences between them, as well as the 152 subjects who did not participate in the imaging study.

There were no significant differences in age between those who underwent β-CIT imaging and those who did not. 51.2% of the subjects used cardiovascular medications; 50.6% took centrally active medications. Based on these demographic variables, we conclude that selection bias is unlikely and that the β-CIT findings can be generalized to the entire cohort. Four men were removed from subsequent analyses, despite a prescreening questionnaire, because the extensive interview revealed that those subjects had suffered a

**Table 1**
Demographic and background characteristics for the β-CIT cohort of study participants and non-β-CIT participants from the GE capacitor worker study ($N=241$).

| Characteristic | β-CIT participants ($N=89$) | | Non-β-CIT participants ($N=152$) | |
|---|---|---|---|---|
| | $N$[a] | Mean ± SEM or % | $N$[a] | Mean ± SEM or % |
| Age (years) | | | | |
| Overall | 89 | 63.5 ± 0.8 | 152 | 64.9 ± 0.7 |
| By sex | | | | |
| Men | 50 | 62.6 ± 0.9 | 79 | 65.1 ± 1.0 |
| Women | 39 | 64.6 ± 1.4 | 73 | 64.8 ± 1.1 |
| Sex | | | | |
| Men | 50 | 56.2 % | 79 | 52.0 % |
| Women | 39 | 43.8 % | 73 | 48.0 % |
| BMI (kg/m$^2$) | | | | |
| Men | 46 | 29.81 ± 0.67 | 76 | 28.60 ± 0.51 |
| Women | 39 | 30.69 ± 1.01 | 72 | 29.60 ± 0.72 |
| Education (school years complete) | | | | |
| Men | 46 | 13.07 ± 0.31 | 76 | 13.11 ± 0.27* |
| Women | 39 | 12.50 ± 0.19 | 73 | 12.29 ± 0.23 |
| Bone lead (μg/g) | | | | |
| Men | 49 | 17.70 ± 1.11 | 74 | 17.65 ± 1.03 |
| Women | 37 | 14.32 ± 1.51 | 70 | 15.37 ± 1.28 |
| Caffeinated beverages past year (drinks) | | | | |
| Men | 46 | 958 ± 85 | 79 | 885 ± 61 |
| Women | 39 | 730 ± 102 | 73 | 943 ± 67 |
| Number of packs of cigarettes in the last 10 years | | | | |
| Men | 46 | 600 ± 218 | 76 | 648 ± 157 |
| Women | 39 | 857 ± 375 | 73 | 872 ± 201 |
| Number of alcoholic drinks per week in the last 10 years | | | | |
| Men | 46 | 5.85 ± 0.97*** | 76 | 7.71 ± 1.23*** |
| Women | 39 | 1.58 ± 0.61 | 73 | 0.90 ± 0.20 |
| Use of cardiovascular drugs[b] | | | | |
| Men | 45 | 66.67 %** | 73 | 61.64 % |
| Women | 39 | 33.33 % | 73 | 46.58 % |
| Use of CNS active medications[c] | | | | |
| Men | 50 | 58.00 % | 79 | 58.23 % |
| Women | 39 | 41.03 % | 73 | 49.32 % |

[a] Number of observations varies across characteristics due to missing values.
[b] Cardiovascular drugs (Class 24) include: antilipemic agents, vasodilating agents, alpha- and beta-adrenergic and calcium-channel blocking agents, and renin–angiotensin–aldosterone system inhibitors.
[c] CNS active medications include: antihistamines, sympathomimetic agents, beta-adrenergic blocking agents, angiotensin-converting enzyme inhibitors, COX-2 inhibitors, other non-steroidal anti-inflammatory agents, opiate agonists, miscellaneous analgesics and antipyretics, thyroid agents and antithyroid agents.
* $p \leq 0.05$, significant difference between men and women within the β-CIT participants or the non-β-CIT-participants.
** $p \leq 0.01$, significant difference between men and women within the β-CIT participants or the non-β-CIT-participants.
*** $p \leq 0.001$, significant difference between men and women within the β-CIT participants or the non-β-CIT-participants.

brain trauma which might affect the outcomes. Additionally, any individual who reported in the initial screening interview that he or she had been diagnosed with PD was excluded from the study.

The imaging cohort consisted of 89 individuals (39 women [44%] and 50 men [56%]), ranging in age from 51 to 85 years (mean = 63.5, SEM = 0.9). There were no significant differences in age between the men and women who participated in the imaging study. Men, however, reported using more cardiovascular medicines ($p<0.01$) than did women and drank alcoholic beverages more often than women ($p<0.001$). There was no significant correlation between the consumption of alcohol and either β-CIT or serum PCBs in the cohort (Table 3).

### *Serum PCB concentrations in men and women former capacitor workers*

The geometric means and standard errors of the mean for serum PCB concentrations (for light, heavy, total and occupational) on a lipid-adjusted basis (ppm) for men and women for the 85 subjects in the β-CIT cohort are shown in Table 2. In the β-CIT cohort, the lipid-adjusted serum total PCB concentration for men was 1.01 ppm ± 1.21 and for women 0.95 ppm ± 4.75. There were no significant differences in any of these measures of exposure between men and women in the β-CIT cohort. In addition, there were no significant differences between β-CIT participants and non- β-CIT participants for any of the PCB measures (data not shown).

### *[$^{123}$I]β-CIT densities decrease with age in both men and women*

The relationship between the age of the subjects and striatal DAT density was determined separately for men and women. As seen in Fig. 1, age was inversely associated with striatal DAT density for both men and women, i.e., as the age of the individuals increased, striatal DAT density decreased regardless of the sex of the individual. Indeed, analysis of variance detected a main effect of age ($F=5.171$, $p=0.02$) but failed to detect either a significant effect of sex ($F=0.346$, $p=0.56$) or a significant age × sex interaction ($F=0.059$, $p=0.809$).

### *Serum total PCB concentrations are inversely associated with striatal [123I]β-CIT densities in women*

The relationship between log serum total PCB concentrations on a lipid-adjusted basis and striatal β-CIT densities, by sex, without statistical adjustment for potential confounders is shown in Fig. 2. Unlike the effects of age, the sex of the individual significantly influenced the relationship between log- and lipid-adjusted total serum PCB concentrations and β-CIT densities. Serum PCB concentrations were statistically significant and inversely related to striatal β-CIT densities for women, but not for men. Indeed, the main effect of sex was significant ($F=5.79$, $p=0.02$) as was the main effect of log total serum PCB concentrations (on a lipid basis), for women ($F=12.93$, $p<0.001$), but not for men ($F=2.69$, $p=0.10$).

### *Correlations between PCBs, β-CIT SPECT, age, sex and other relevant variables*

We next determined whether the above described relationship between log-adjusted serum PCB concentrations and striatal β-CIT densities persisted after correction for classical confounders (i.e., those statistically associated with both exposure and outcome) as well as other confounders (i.e., variables associated with either exposure or outcome). The results of these analyses are shown in Table 3. Confounders that were statistically associated with both exposure and outcome included age, body mass index (BMI), DDT

**Table 2**
Current lipid-adjusted serum PCB concentrations by sex in individuals that underwent β-CIT SPECT imaging and are included in the final data analysis.

| PCB congener | β-CIT participants ($N=85$) | |
|---|---|---|
| Grouping | Geometric mean | SEM |
| Men ($N=46$) | | |
| Total PCBs | 1.01 | 0.18 |
| Light PCBs[a] | 0.39 | 0.12 |
| Heavy PCBs[b] | 0.55 | 0.08 |
| Occupational PCBs[c] | 0.28 | 0.13 |
| Women ($N=39$) | | |
| Total PCBs | 0.95 | 0.76 |
| Light PCBs[a] | 0.38 | 0.37 |
| Heavy PCBs[b] | 0.52 | 0.44 |
| Occupational PCBs[c] | 0.31 | 0.43 |

[a] Elute before DDE.
[b] Elute after DDE.
[c] Markers for occupational exposure.

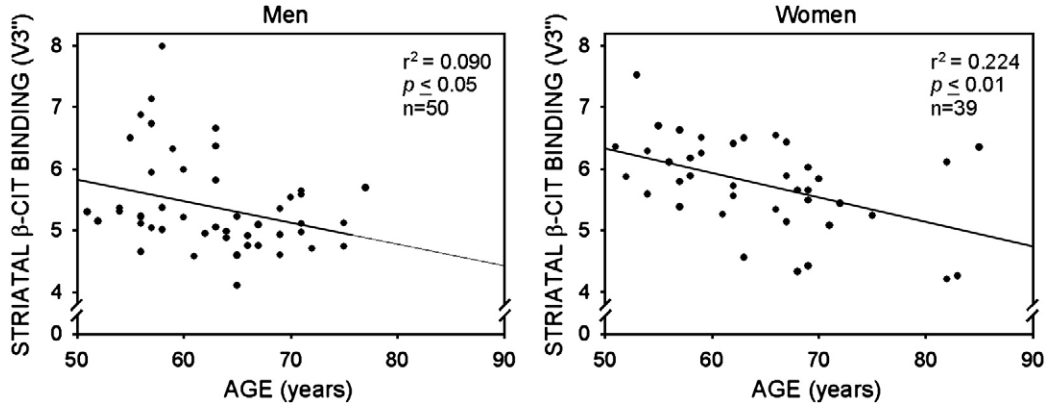


**Fig. 1.** Dopamine transporter density measured by β-CIT SPECT imaging as a function of age by sex in former capacitor factory workers.

levels and total serum lipids (expressed as gm/l). When these variables were included as potential confounders in a univariate analysis of variance, the relationship between log total lipid-adjusted serum PCBs for women was still significant ($F=5.37$, $p=0.02$) while the relationship between log total serum PCBs for men was not ($F=0.36$, $p=0.55$). Successive univariate analyses, where confounders shown to be non-significant were removed, resulted in a final analysis of variance that included age, BMI and sex. The resulting statistical association between log total serum PCB concentrations (on a lipid basis) and striatal β-CIT densities remained highly significant for women ($F=6.16$, $p=0.015$), but not for men ($F=0.10$, $p=0.75$) and is presented in Fig. 3. In summary, the inverse relationship between serum PCB levels and DAT density, observed only in women, remained highly significant even after adjusting, for example, for the effects of age which is correlated both with a decrease in β-CIT binding as well as increased serum PCB levels.

Similar findings were also seen between log- and lipid-adjusted serum total PCB concentrations and either putamen or caudate β-CIT densities. For the putamen, β-CIT densities for women were significantly and inversely related to log total serum PCB concentrations (on a lipid basis) ($F=5.46$, $p=0.02$), but not for men ($F=0.19$, $p=0.67$). For the caudate, β-CIT densities for women were significantly and inversely related to log total serum PCB concentrations (on a lipid basis) ($F=5.83$, $p=0.02$); again, that was not the case for men ($F=0.75$, $p=0.39$).

We also examined whether the class of PCBs—i.e., light, heavy or occupational—altered the statistical relationships described between total serum PCB concentrations and β-CIT densities. For each of the sub-classes described above, the significant and inverse relationship between serum PCB concentrations and β-CIT densities remained for women but not for men (data not shown).

## Discussion

We demonstrate that, following long-term occupational exposure to PCBs and after statistical correction for a number of confounders, including age, only women show a significant inverse relationship between lipid-adjusted total serum PCB concentrations and caudate, putamen or combined caudate and putamen β-CIT densities despite the fact that neither serum PCB levels nor age was statistically different between men and women. These findings support, in part, our previously published results obtained in non-human primates (Seegal et al., 1991) demonstrating that long-term exposure to PCBs significantly reduced basal ganglia DA concentrations.

Although the reductions in striatal and putamenal [$^{123}$I]β-CIT densities in women former capacitor workers were statistically significant, the values for [$^{123}$I]β-CIT striatal uptake for all subjects, on an age-corrected basis, were within the normal range based on comparisons to an existing database of 73 healthy adult subjects at the same imaging center (Jennings et al., 2004). Having said that, the data presented in Fig. 3 demonstrate, after statistically controlling for age and body mass index, a maximal reduction of between 20 and 25% in striatal β-CIT binding in PCB-exposed women. A reduction of this magnitude is unlikely to be associated with clinical signs of parkinsonism. Indeed, none of the individuals exhibited clinical signs of disease due, perhaps, to the exclusion of individuals who reported that they had been diagnosed with PD. Nevertheless, these reductions may serve as an early marker of disease and would warrant

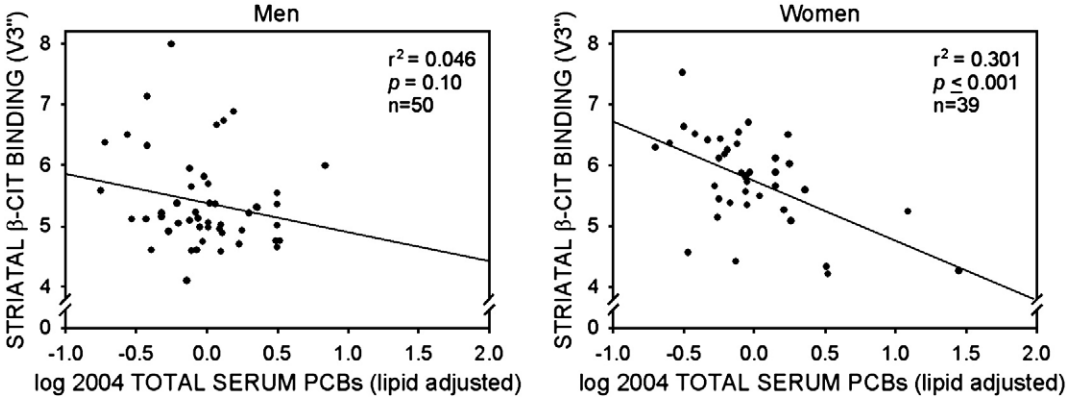


**Fig. 2.** Dopamine transporter density measured by β-CIT SPECT imaging as a function of the log of current serum PCB concentrations (expressed on a lipid-adjusted basis, ppm) by sex prior to adjusting for potential confounders in former capacitor factory workers.

**Table 3**
Correlations between β-CIT, PCBs and classical confounders and other potential confounders in the β-CIT study cohort.

| Confounder | N[a] | β-CIT | | Serum PCBs | |
|---|---|---|---|---|---|
| | | Correlation | p | Correlation | p |
| Serum PCBs | 89 | −0.322 | 0.002 | | |
| β-CIT | 89 | | | −0.322 | 0.002 |
| Sex | 89 | 0.242 | 0.022 | 0.029 | 0.785 |
| Age | 89 | −0.338 | 0.001 | 0.273 | 0.010 |
| Body mass index | 85 | −0.192 | 0.078 | 0.148 | 0.177 |
| Serum DDE | 89 | −0.315 | 0.003 | 0.305 | 0.004 |
| Serum DDT | 89 | −0.201 | 0.059 | 0.681 | 0.001 |
| Serum lipids | 89 | 0.261 | 0.013 | −0.218 | 0.040 |
| Use of cardio medications | 84 | −0.214 | 0.050 | 0.001 | 0.992 |
| Education | 85 | −0.063 | 0.566 | −0.110 | 0.314 |
| Bone lead | 86 | −0.006 | 0.960 | −0.083 | 0.448 |
| Income | 83 | −0.093 | 0.401 | −0.012 | 0.916 |
| Caffeinated drinks (past year) | 78 | 0.084 | 0.467 | 0.016 | 0.892 |
| Alcoholic drinks (past year) | 85 | −0.053 | 0.629 | 0.051 | 0.643 |
| Alcoholic drinks (past 10 years) | 85 | −0.086 | 0.431 | 0.038 | 0.727 |
| Cigarette packs (past year) | 85 | 0.009 | 0.934 | 0.090 | 0.412 |
| Cigarette packs (past 10 years) | 85 | 0.054 | 0.621 | 0.027 | 0.806 |
| Use of CNS active medications | 78 | 0.099 | 0.388 | 0.053 | 0.646 |
| Use of NSAIDS | 78 | −0.032 | 0.784 | −0.037 | 0.750 |
| TSH | 54 | −0.121 | 0.384 | 0.263 | 0.055 |
| T4 | 54 | 0.049 | 0.727 | 0.056 | 0.689 |
| FT4 | 54 | −0.041 | 0.771 | 0.058 | 0.677 |
| T3 | 54 | −0.090 | 0.519 | 0.073 | 0.598 |
| FT3 | 54 | −0.212 | 0.124 | 0.146 | 0.292 |

[a] Number of observation varies across variables due to missing values.

further follow-up. Finally, only a single scan was acquired in our study, hence we lack the temporal data necessary to determine whether subjects with high serum PCB levels would show a more rapid decline in [$^{123}$I]β-CIT striatal uptake with increasing age than either subjects who had not been occupationally exposed to PCBs or workers exposed only to low concentrations of PCBs. Nevertheless, our present results and the observations of Steeenland et al. (2006) and Prince et al. (2006) suggest that occupationally exposed women are at a heightened risk of developing PD.

There are several possible reasons for the disparate results between men and women obtained by us and Steenland et al. (2006) and Prince et al. (2006). First, those prior studies gathered data from all former capacitor workers, including deceased individuals. We, obviously, could obtain [$^{123}$I]β-CIT striatal imaging data only from living individuals. Second, our study was limited to individuals who agreed to participate; thus bias may have been introduced into our study since we could obtain imaging data only from individuals healthy enough to travel from upstate New York to New Haven, CT. Finally, as mentioned above, we excluded anyone diagnosed with PD; thereby limiting the range of changes in basal ganglia function associated with PCB exposure.

The reported alterations in basal ganglia DA function are surprising because they stand in contrast to the large number of epidemiological studies that show that the incidence of idiopathic PD is approximately twice as great in men as in women (Ragonese et al., 2004). In addition, many experimental studies have demonstrated neuroprotection in female rodents following exposure to a number of DA neurotoxicants, including 6-OHDA and MPTP (Dluzen, 2000), compared to male rodents (Miller et al., 1998). These sex differences in susceptibility are thought to be due to the actions of ovarian hormones, since supplementation of ovariectomized animals, particularly with estrogen, partially ameliorates reductions in measures of central DA integrity. Hence, based on both experimental and epidemiological findings, one would predict that men, rather than women, would show greater reductions in basal ganglia DA terminal densities following occupational exposure to PCBs.

What potential mechanisms may be responsible for the greater sensitivity of women to PCBs in this study? One potential explanation is based on the work of Bossé et al. (1997) who showed that ovariectomy reduces [$^{3}$H] GBR-12935 binding in the striatum, suggesting a reduction in either the density or function of the DAT. In addition, Mariussen and Fonnum (2001) and Bemis and Seegal (2004) have shown that PCBs inhibit the DAT. Given the importance of this transporter in regulating both intra- and extra-synaptosomal DA concentrations and the consequences of such inhibition (Cyr et al., 2003; Jaber et al., 1997), modulation of DAT density or function by postmenopausal reductions in central estrogen may interact with PCBs resulting in a loss of function greater than either menopause or PCBs alone.

We further suggest that age-related decline in central gonadal hormones, either of ovarian origin or conversion of testosterone to estrogen (Barreto et al., 2009; Veiga et al., 2004), has different consequences in men and women following exposure to known DA neurotoxicants. This suggestion is supported by data from Murray et al. (2003) and Tamas et al. (2005) who have shown that following 6-OHDA: (i) ovariectomy increases the loss of basal ganglia DA, compared to that seen in the intact female; (ii) castration reduces the loss of basal ganglia DA, compared to that seen in the intact male; (iii) estrogen supplementation in the ovariectomized rat restores DA to levels seen in the intact female and (iv) estrogen supplementation in the castrated male *reduces* the protection following castration to levels seen in the intact male rat. These findings suggest that central estrogen is neuroprotective in the female while estrogen (from aromatization of testosterone) may be a risk factor in the male brain. Thus, reductions in ovarian hormones following menopause (all women in this study were postmenopausal) are posited to result in the loss of known neuroprotective factor(s) (i.e., estrogen and progesterone) while reductions in circulating testosterone and central

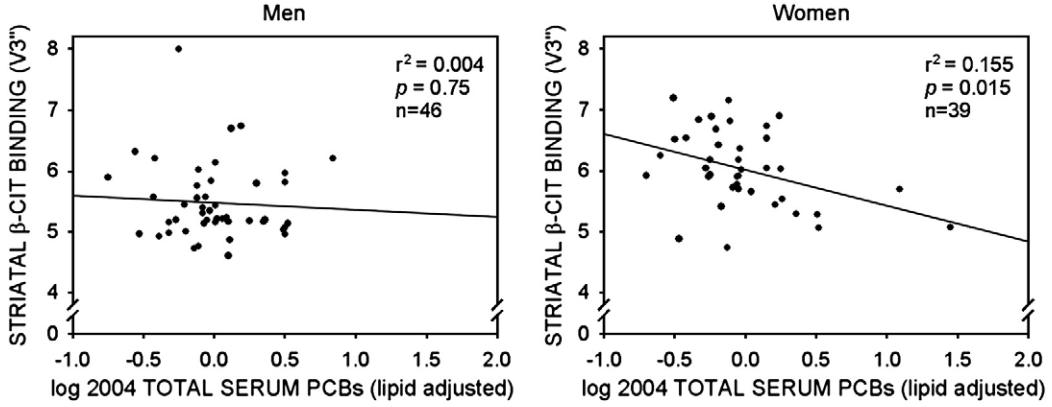


**Fig. 3.** Dopamine transporter density measured by β-CIT SPECT imaging as a function of the log of current serum PCB concentrations (expressed on a lipid-adjusted basis, ppm) by sex after adjusting for age and BMI in former capacitor factory workers.

aromatase activity in the aging male may result in the loss of a neuro-risk factor (i.e., central estrogen). For this hypothesis to provide a viable explanation for the sex differences in the effects of occupational exposure to PCBs on caudate and putamen β-CIT SPECT binding, it is necessary to posit that, if we had conducted the imaging study in younger, reproductively competent workers, we would have found that men would be more affected by PCB exposure than women. In partial support of this, we have recently shown that PCB exposure leads to greater loss of striatal DA in reproductively competent male rodents than in similarly aged female rodents.

There are inherent limitations in the ability to extrapolate findings from any study using experimental animals to humans that may weaken our ability to explain the findings from this study. For example, the rats in the Murray et al. (2003) and Tamas et al. (2005) studies underwent gonadectomy prior to exposure to 6-OHDA, while the former capacitor workers in our study were exposed to PCBs while they were still reproductively competent. Nevertheless, the results are intriguing and support the findings of both Steenland et al. (2006) and Prince et al. (2006) who report an increase in PD-associated mortality in highly exposed women but not in men. We must emphasize that the results presented here were obtained in a fairly small number of workers and it would be highly desirable to increase the number of observations to include other cohorts of individuals who had been either occupationally or inadvertently exposed to PCBs, as well as younger, highly exposed individuals.

In summary, we find that elevations in lipid-adjusted total serum PCB concentrations, due to long-term occupational exposure, are inversely associated with measures of DAT density in women, but not in men despite the lack of significant differences in serum PCB levels between the men and women and statistical adjustment for age. We suggest that the combination of age-related changes in ovarian hormone levels and exposure to high levels of PCBs, both known to alter DAT function (Bemis and Seegal, 2004; Bossé et al., 1997; Mariussen and Fonnum, 2001) and the viability of DA neurons (Leranth et al., 2000; Lyng et al., 2007; Seegal et al., 1994b), results in the somewhat paradoxical finding that reproductively senescent women, but not men, account for the significant relationship between current serum PCB levels and reductions in striatal DAT binding. Finally, the unexpected results of this study not only emphasize the need to consider sex as an important variable in determining the central response(s) to known and suspected neurotoxicants but also suggest broadening the definition of gene × environment interactions to include sex.

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# Estimating the half-lives of PCB congeners in former capacitor workers measured over a 28-year interval

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To date, most estimates of the half-life of polychlorinated biphenyls (PCBs) in humans have been based on relatively short follow-up periods. To address this issue, we determined the half-lives of PCB congeners of occupational origin in the serum of former capacitor workers as part of a study conducted in 2003–2006 — approximately 28 years after their last occupational exposure. A total of 241 persons from a source population of 6798 former capacitor workers were interviewed and asked to donate a blood sample for serum PCB congener analysis. A subgroup of 45 participants also had serum archived from 1976 and reanalyzed for the same 27 PCB congeners by the same laboratory. Our estimates of the half-lives of the congeners among these 45 persons were longer than those reported by Wolff et al. (1992), due primarily to the much longer interval between exposure and determination of serum PCB concentrations. Half-lives were significantly greater for the heavy *versus* light occupational congeners, for women *versus* men and for those with low *versus* high initial exposure. Current serum total PCB concentrations, expressed as the geometric mean of wet weight data, averaged 6.7 ng/g for the entire 241-person cohort, which represents a 10-fold decrease from values reported in the late 1970s, but is still nearly twice the average for persons of similar age residing in the same area, but without occupational exposure. In addition, current serum PCB concentrations remained significantly and positively associated with earlier occupational exposure, but were not associated with fresh water fish consumption. In general, the results support a consistent and long-duration trend of increased PCB body burden in this cohort of former capacitor workers compared with non-occupationally exposed individuals. The results may aid in further understanding the toxicological/epidemiological consequences of exposure to PCBs in humans.
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**Keywords:** *occupational exposure, polychlorinated biphenyls, half-lives, adults.*

## Introduction

Polychlorinated biphenyls (PCBs) are halogenated aromatic hydrocarbons with unique physical and chemical properties including thermal stability, resistance to acids, oxidation, hydrolysis, and low vapor pressure (ATSDR, 2000). They were produced by the Monsanto Company (St. Louis, MO, USA) under the Aroclor trade name and were used by the General Electric Company (GE) in two facilities in Fort Edward and Hudson Falls, New York in the manufacture of electrical capacitors beginning in 1946 until 1977 (National Research Council, 1979). Aroclor 1254 was used initially; however, beginning in 1953, Aroclor 1242 was used for all manufacturing with the exception of some specialty capacitors. In 1971, Aroclor 1242 was replaced with Aroclor 1016, while a small amount of Aroclor 1221 was used in the later years, that is, through 1977 (Fischbein et al., 1979). Air concentrations of PCBs in direct exposure job areas in 1977, just prior to the end of PCB use, were approximately 310 $\mu g/m^3$, whereas levels of PCBs in indirect exposure job areas were 10-fold lower (27 $\mu g/m^3$) (Taylor et al., 1991). Areas surrounding the plant had an

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average air PCB concentration of 6.2 $\mu g/m^3$ (Taylor et al., 1991), whereas ambient air concentrations in urban areas distant from the plants averaged 0.1 $\mu g/m^3$ (Kutz and Yang, 1975).

Fischbein et al. (1979) analyzed sera from 310 workers in these facilities in 1976 and found that they were, on average, 10- to 20-fold higher than in the general population (Wolff et al., 1982; Lawton et al., 1985). A subgroup of our cohort also had sera archived from 1976, allowing us to compare PCB concentrations and estimate their half-lives over a 28-year period. Although half-lives for PCBs have been estimated previously in these workers (Wolff et al., 1992), they were estimated after less than 5 years of follow-up — in fact, to our knowledge no other study has evaluated PCB half-lives over nearly 30 years. In addition, we also assessed variations in current PCB concentrations among all persons in the recreated cohort according to sociodemographic factors, past occupational exposure, and fish consumption. The results presented here are from a larger project designed to evaluate the neurobehavioral effects of PCBs. The rationale was that, although PCBs have been associated with deficits in behavior and cognitive performance in infants and children (Jacobson and Jacobson, 2003; Gray et al., 2005; Stewart et al., 2005), recent epidemiological findings from Schantz et al. (1996, 2001) and Fitzgerald et al. (2008) also suggest changes in the behavior of older adults.

## Methods

*Study Population*

The study population was recruited between 2003 and 2006 and consisted of former capacitor workers who had been employed by GE for at least 3 months between 1946 and 1977 at either of two capacitor factories. This population was identified based on information generated in the 1970s by the New York State Department of Health (NYSDOH), in cooperation with GE and the National Institute of Occupational Safety and Health. Information included names, dates of birth, gender, social security number, job codes, and start and end dates for most jobs held by the 6798 former workers (3784 men and 3014 women). This cohort is believed to reflect virtually all persons who worked at the facilities in the time frame of interest.

*Human Subjects Protection*

Prior to initiation of the study, the design and instruments, including those associated with tracing, screening, recruitment, and data collection, were reviewed and approved by Institutional Review Boards at each of the study's collaborating institutions (NYSDOH, Albany Medical Center, University at Albany, Institute for Neurodegenerative Disorders and the U.S. Army).

*Inclusion Criteria*

To be considered for inclusion in the study, former workers had to: (i) currently live within a 100-mile radius of Albany, NY, USA; (ii) have worked at GE for at least 3 consecutive months between 1946 and 1977; and (iii) be at least 50 years of age. We oversampled certain categories of individuals, including those who had been previously tested by researchers from the Mount Sinai School of Medicine in the 1970s (Fischbein et al., 1979), and thus had sera archived from that period ($N = 310$), as well as workers who had held job(s) considered to place them at risk for high-level exposure to PCBs ($N = 589$). Finally, in the last 2 years of the study, we made efforts to oversample women to ensure that adequate numbers were available for statistical analyses stratified by gender.

*Interview Assessment*

Study participants were interviewed in person. Demographic information included education, race, ethnicity, marital status, gender, income, and residential history. A dietary history was also collected that included information on consumption of sport-caught fish, dairy products, and caffeinated beverages. In addition, the number and type of jobs held both at GE and elsewhere, as well as selected non-occupational activities and hobbies (e.g., stained glass making, painting), likely to result in exposure to neurotoxicants and lifestyle characteristics (smoking, alcohol consumption, and physical activity), were also collected. Finally, a comprehensive medical history, including use of over-the-counter and prescription drugs, as well as (if applicable) female reproductive histories (the number of pregnancies, breastfeeding history, and menopausal status) was collected.

*Serum PCB Analysis*

All samples, including current and archived sera, were analyzed for PCBs using the current methodologies of Gammon et al. (2002) based on the methods described by Brock et al. (1996). Quality control was monitored using three plasma pools fortified with PCB congeners corresponding to 0, 5, or 10 ng/ml total PCB. Detection limits (0.07 $\mu g/l$ per congener (Gammon et al., 2002)) were based on three times the SD of results from blanks and from the unfortified pool, which contained approximately 1 ng/ml each of DDE and of total PCBs. The higher detection limit compared with NHANES (CDC, 2005) is due to the analytic method, that is, the use of GC-ECD instead of GC-MS. Values less than the detection limit were set to the lowest positive value for a given analyte. This decision was based on the fact that many chemists and statisticians believe that a reported result, even if it is below the "criterion for detection," is the best available estimate of the true value, and is preferable to assigning a zero or an arbitrary constant, such as one-half the detection limit (Wolff et al., 2008; Fitzgerald et al., 2007b). Coefficients of variation (SD/mean) of DDE and PCBs

from the fortified pools were 10% to 15%. To ensure comparability between the current and historic serum PCB measurements for half-life estimation, archived sera from 1976 was reanalyzed using the same analytic methods described above for the current samples.

Total serum PCB concentration was defined as the sum of the 27 individual congeners that were analyzed. We also determined serum concentrations of ''light'' PCBs, that is, those congeners eluting before DDE; ''heavy'' PCBs, that is, those congeners eluting after DDE; and ''occupational'' PCB congeners, as previously defined by Wolff et al. (1982). Wolff M.S. (personal communication) identified PCB congeners 28, 74, 118, 105, and 156 as unique markers of occupational exposure based on demonstration that levels of these congeners are low in the general population and are derived almost exclusively from the Aroclor mixtures used in the capacitor plants.

We determined total serum lipid concentrations for samples collected in the period from 2003 to 2006 using the algorithm of Phillips et al. (1989a) to calculate total lipids from serum cholesterol and triglycerides. Results are expressed on both a wet weight and lipid basis for the current serum PCB concentrations to allow comparison of PCB levels with other published studies. Because of issues surrounding the accuracy of the measurement of lipid levels in the reanalyzed archived sera and the goal of comparing our half-life calculations with the published data of Wolff et al. (1992) which were based on wet weight data, we present all PCB data from the archived cohort subjects on a wet weight basis. This decision is supported by the fact that we are comparing paired data from the same individual at two time periods.

*Fresh Water Fish Consumption*

The exposure assessment for fish consumption focused on the Hudson River and other bodies of fresh water in New York State known to be contaminated with PCBs. Surveys conducted by the New York State Department of Environmental Conservation indicate that, in addition to the Hudson River, sport fish caught from Lakes Ontario and Champlain are also heavily contaminated with PCBs. These findings have resulted in bans or advisories against consumption of many fish species from those bodies of water being repeatedly issued by the NYSDOH (http://www.health.state.ny.us/nysdoh/environ/fish/htm).

Relatively few persons in our study consumed fish from the Hudson River. Hence, these data were combined with consumption data from Lakes Ontario and Champlain, the two most common sources of sport fish consumption for study participants, and other New York bodies of fresh water to provide a summary measure of fish consumption. This measure was computed by multiplying the yearly consumption rate of fresh water fish by the number of years fish were consumed for each of three time periods (before 1994, 1994 to the year before the interview, and the last year) and summed to estimate total cumulative exposure to PCBs from fresh water fish consumption. Persons who consumed fresh water fish from these bodies of water were then divided into groups above and below the median consumption value and compared with those who did not consume such fish. These consumption data were collapsed across species because species-specific fish PCB levels were not available for all the time periods of interest. This metric did not provide for individual estimates of PCB intake through fish consumption, but did allow for a semiquantitative comparison of serum PCB concentrations according to relative fish consumption.

*Occupational Exposure to PCBs*

Potential occupational PCB exposure was assessed by two industrial hygienists (IHs) who independently rated the probability of exposure for all GE jobs held for 3 or more months and all non-GE jobs held for more than 1 year. These assessments were based on the name(s) and location of the company, type of industry, and a brief description of work duties reported during the interview assessment. The IHs assigned one of four qualitative ratings to each self-reported job: (1) definitely not exposed, (2) possibly exposed, (3) probably exposed, and (4) definitely exposed. These ratings were then assigned weights of 0, 0.25, 0.5, and 1.0, respectively. When IH ratings differed, the IHs jointly reviewed the data and came to agreement on a rating. The weights for each job then were multiplied by how long the participant worked in that job, and the results were summed over all jobs to estimate total cumulative occupational exposure to PCBs for each participant. Occupational exposure was also partitioned according to the years when specific Aroclors were used by GE, that is, 1946–1953 for Aroclor 1254, 1953–1971 for Aroclor 1242, and 1971–1977 for Aroclor 1016 (with minor Aroclor 1221 usage) (Lawton et al., 1985).

*Half-life Estimation*

In order to estimate the half-lives (hl) of the PCB congeners for the 45 participants for whom we had both current serum as well as serum archived from 1976, we assumed an exponential decay model ($C_{(t)} = C_{(0)}e^{-kt}$) (Friedman, 1979) to describe the metabolism/excretion of PCBs across the 28-year span using methods previously used by Taylor and Lawrence (1992); Phillips et al. (1989b); and Shirai and Kissel (1996). In this model, $C_{(t)}$ represents the 2004 serum PCB measures, $C_{(0)}$ represents the 1976 serum PCB measures, $t$ is the 28-year time interval, and $k$ represents the decay constant. Since the value of $(\ln(C_{(0)}) - \ln(C_{(t)}) = kt)$ is known and with $k = \ln(2)/hl$, then it follows that the half-life of the PCBs can be estimated by $hl = \ln(2)*t/\ln(C_{(0)}) - \ln(C_{(t)})$. Different authors recommend different estimates of the $C_0$ and $C_t$, including either the median or

the geometric mean of the PCB quantities across the sample. As these two estimators are often very close in value, we chose the geometric mean to estimate the value of $C_0$ and $C_t$ in this research. We did not have specific determinations of PCB intake from fish consumption or other foodstuffs to incorporate into our half-life estimates, so the half-life computations were restricted to those congeners that were occupational in origin, that is, PCB-28, 74, 118, 105, and 156.

*Statistical Analysis*

Rank transformation analysis of variance tests of simple main effect differences were used to compare calculated half-lives between men and women and exposure levels for the above described PCB congener groups. Multiple linear regression analysis was also used to test for associations between current serum PCB levels and demographic and background variables (age, gender, education, body mass index (BMI), marital status, cigarette smoking, alcohol consumption, and prescription drug use, some of which have been related to serum or plasma PCB levels in other studies (Rylander et al., 1997; Moysich et al., 2002). Variables found to be significant in a bivariate analysis were then regressed on the log-transformed serum total PCB concentration using stepwise procedures to add or remove the background variables one at a time. Cumulative exposure to PCBs from occupation and fresh water fish consumption were then added to the regression models to estimate their associations with current serum total PCB concentrations after adjustment for all remaining background variables.

## Results

*Recruitment and Participation*

The population of former capacitor workers on computer tapes made available to us consisted of 6798 individuals; 6398 of these were retained as the potential pool of individuals to trace on the basis of a documented employment history at GE between 1946 and 1977. A total of 2844 (44%) were selected for tracing according to our previously discussed criteria. Of this group, 844 (30%) were deceased; 256 (9%) either lived beyond a 100-mile radius of Albany or had worked at either of the capacitor facilities for a period of less than 3 months during the specified time period; and 577 (20%) could not be located. In addition, 43 (2%) of those selected for tracing were not ultimately traced because they were selected for tracing just before the completion of the study.

The remaining 1124 persons (40%) were contacted by telephone and screened for eligibility. Forty-two individuals (4%) refused to participate in the screening interview; 110 (10%) agreed to answer the screening interview but refused to be contacted for recruitment into the study; and 80 (7%) never returned our screening telephone calls, despite numerous attempts. In addition, 348 of those screened (31%) were deemed ineligible for the medical reasons. Since the larger project focused on nervous system function, these persons included those diagnosed with or treated for conditions such as multiple sclerosis, stroke, head injury, epilepsy, or psychiatric disorders. Fifty individuals (5%) were considered ineligible because of their inability to travel to the study sites or complete the study measures, and 10 (1%) were entered into screening just before the conclusion of the study and were thus not screened.

The other 484 (43%) were eligible for participation in the study. Approximately half of these refused, while the remaining half agreed to participate in the study yielding a final study population of 241 persons. Compared with the 6157 former workers not enrolled in the study, the participants were significantly younger (38 years old as of 1 January 1978 *versus* 45 years old for the non-participants, $P \leq 0.001$) and more likely to be highly exposed to PCBs according to the job histories available from the computer tapes (25% *versus* 10% for the non-participants, $P \leq 0.001$; data not shown). There were no differences by gender.

Of the 241 former workers in this study, 33 men and 12 women also participated in the 1976 study conducted by Fischbein et al. (1979). Table 1 presents the demographic and background characteristics for both the entire cohort ($N = 241$) and for that subset with both current and archived serum ($N = 45$). The subgroup with archived sera was generally similar to the full cohort with the exception of the age of the women at the time that they were interviewed for this study (greater in the archived cohort) and the number of children (again greater in the archived cohort). BMI was lower in the women in the archived subgroup compared with the larger sample.

*Current Serum PCB Concentrations*

Current serum geometric mean PCB concentrations, for men and women separately, expressed on both a wet weight basis (ng/g) and a lipid adjusted basis ($\mu$g/g) are presented in Table 2. Total current serum PCB concentration for men was 7.47 ng/g or 1.19 $\mu$g/g. For women the corresponding values were 5.81 ng/g or 0.86 $\mu$g/g. For men $\sim$61% of the total PCB residue in serum consisted of heavily chlorinated PCBs (those eluting after DDE), most notably PCB congeners 153, 180, and 138. For women $\sim$55% of the total PCB residue consisted of heavily chlorinated PCBs. Men (Table 2a) had significantly higher serum concentrations of both heavy congeners ($P \leq 0.01$) and total PCBs ($P \leq 0.01$) than did women (Table 2b).

*Predictors of Current Serum PCB Concentrations*

Age was the demographic variable most strongly associated with log current serum total PCB concentrations ($\beta = 0.015$, $P \leq 0.001$, data not shown). Log current serum total PCB concentrations were also higher among men than women

**Table 1.** Demographic and background characteristics of all study participants ($N = 241$) and the cohort of subjects with archived sera ($N = 45$).

| Characteristic | All study participants | | Archived sera cohort | |
|---|---|---|---|---|
| | % or Mean (SD) | N[a] | % or Mean (SD) | N[a] |
| *Gender* | | | | |
| Male | 53.6 | 129 | 73.3 | 33 |
| Female | 46.5 | 112 | 26.7 | 12 |
| *Income* | | | | |
| <15,000 | 9.0 | 20 | 2.2 | 1 |
| 15,000–30,000 | 22.4 | 50 | 37.8 | 17 |
| 30,000–45,000 | 26.5 | 59 | 13.3 | 7 |
| 45,000–60,000 | 18.8 | 42 | 15.6 | 7 |
| 60,000–75,000 | 13.0 | 29 | 15.6 | 7 |
| >75,000 | 10.3 | 23 | 0 | 0 |
| *Marital status* | | | | |
| Married or live with partner | 70.5 | 165 | 73.2 | 30 |
| Divorced, never married, separated, or widowed | 29.5 | 69 | 26.8 | 11 |
| *Lost weight in past year* | | | | |
| No | 80.8 | 189 | 80.5 | 33 |
| Yes | 19.2 | 45 | 19.5 | 8 |
| *Had hepatitis or cirrhosis of the liver* | | | | |
| No | 97.0 | 225 | 97.5 | 39 |
| Yes | 3.0 | 7 | 2.5 | 1 |
| *Age (years)* | | | | |
| Male | 64.1 (8.1) | 129 | 64.0 (7.8) | 33 |
| Female | 64.7 (9.3) | 112 | 70.5 (8.6)* | 12 |
| *Education (school years completed)* | | | | |
| Male | 13.1 (2.2)++ | 122 | 12.7 (1.2)+ | 29 |
| Female | 12.4 (1.7) | 112 | 12.2 (0.9) | 12 |
| *BMI ($kg/m^2$)* | | | | |
| Male | 29.1 (4.5) | 122 | 28.6 (3.9)+ | 29 |
| Female | 29.9 (6.1) | 112 | 25.9 (3.5)** | 12 |
| *Number of cigarette packs in the previous year* | | | | |
| Male | 38.4 (111.4) | 122 | 44.1 (116.1) | 29 |
| Female | 46.6 (122.8) | 112 | 121.8 (179.9) | 12 |
| *Number of cigarette packs in the last 10 years* | | | | |
| Male | 630 (1404) | 122 | 557 (1191)+ | 29 |
| Female | 867 (1946) | 112 | 2100 (3169) | 12 |
| *Total number of drinks/week in the last year* | | | | |
| Male | 6.84 (9.16)+++ | 122 | 8.24 (9.9)+ | 29 |
| Female | 1.47 (3.46) | 112 | 1.86 (4.0) | 12 |
| *Total number of drinks/week in the last 10 years* | | | | |
| Male | 7.01 (9.38)+++ | 122 | 8.50 (9.35)++ | 29 |
| Female | 1.14 (2.62) | 112 | 1.05 (1.37) | 12 |
| Number of births (females only) | 2.71 (1.63) | 112 | 3.75 (2.14)* | 12 |
| Total weeks lifetime breastfeeding (females only) | 7.18 (22.73) | 112 | 6.92 (20.59) | 12 |

[a]Number of observations varies across characteristics due to missing values.
* The $t$-test or $\chi^2$ is significant at $P \leq 0.05$ for all study participants vs archived sera cohort.
** The $t$-test or $\chi^2$ is significant at $P \leq 0.01$ for all study participants vs archived sera cohort.
+ The $t$-test or $\chi^2$ is significant at $P \leq 0.05$ for male vs female.
++ The $t$-test or $\chi^2$ is significant at $P \leq 0.01$ for male vs female.
+++ The $t$-test or $\chi^2$ test is significant at $P \leq 0.001$ for male vs female.

**Table 2a.** Current serum PCB concentrations in men who participated in the study ($N = 129$).

| IUPAC number | IUPAC structure | % of non-detectable or zero values | Wet weight (ng/g) | | Lipid basis ($\mu$g/g) | |
|---|---|---|---|---|---|---|
| | | | Geometric mean | SD | Geometric mean | SD |
| *Light PCBs*[a] | | | | | | |
| PCB-28[b] | 2,4,4′ | 25.6 | 0.07 | 0.52 | 0.01 | 0.09 |
| PCB-74[b] | 2,4,4′,5 | 1.6 | 1.01 | 5.18 | 0.16 | 0.80 |
| PCB-66 | 2,3′,4,4′ | 17.8 | 0.14 | 0.33 | 0.02 | 0.05 |
| PCB-56 | 2,3,3′,4′ | 13.2 | 0.11 | 0.20 | 0.02 | 0.04 |
| PCB-101 | 2,2′,4,5,5′ | 3.1 | 0.29 | 0.50 | 0.05 | 0.09 |
| PCB-99 | 2,2′,4,4′,5 | 5.4 | 0.15 | 0.40 | 0.02 | 0.07 |
| Total | | | 2.84 | 5.83 | 0.45 | 0.92 |
| *Heavy PCBs*[c] | | | | | | |
| PCB-118[b] | 2,3′,4,4′,5 | 8.5 | 0.16 | 0.73 | 0.03 | 0.14 |
| PCB-146 | 2,2′,3,4′,5,5′ | 1.6 | 0.09 | 0.22 | 0.01 | 0.04 |
| PCB-153 | 2,2′,4,4′,5,5′ | 0.0 | 0.90 | 1.70 | 0.14 | 0.29 |
| PCB-105[b] | 2,3,3′,4,4′ | 17.1 | 0.04 | 0.17 | 0.01 | 0.03 |
| PCB-138 | 2,2′,3,4,4′,5′ | 0.8 | 0.73 | 1.37 | 0.12 | 0.23 |
| PCB-178 | 2,2′,3,3′,5,5′,6 | 9.3 | 0.04 | 0.10 | 0.01 | 0.02 |
| PCB-187 | 2,2′,3,4′,5,5′,6 | 3.1 | 0.14 | 0.21 | 0.02 | 0.04 |
| PCB-183 | 2,2′,3,4,4′,5′,6 | 4.7 | 0.07 | 0.06 | 0.01 | 0.01 |
| PCB-167 | 2,3′,4,4′,5,5′ | 16.3 | 0.03 | 0.08 | 0.004 | 0.02 |
| PCB-174 | 2,2′,3,3′,4,5,6′ | 7.8 | 0.05 | 0.05 | 0.01 | 0.01 |
| PCB-177 | 2,2′,3,3′,4,5′,6′ | 11.6 | 0.04 | 0.07 | 0.01 | 0.01 |
| PCB-156[b] | 2,3,3′,4,4′,5 | 0.8 | 0.19 | 0.59 | 0.03 | 0.09 |
| PCB-172 | 2,2′,3,3′,4,5,5′ | 7.8 | 0.07 | 0.10 | 0.01 | 0.02 |
| PCB-180 | 2,2′,3,4,4′,5,5′ | 0.8 | 0.51 | 1.05 | 0.08 | 0.18 |
| PCB-170 | 2,2′,3,3′,4,4′,5 | 2.3 | 0.23 | 0.48 | 0.04 | 0.08 |
| PCB-199 | 2,2′,3,3′,4,5,5′,6′ | 0.0 | 0.11 | 0.15 | 0.02 | 0.03 |
| PCB-203 | 2,2′,3,4,4′,5,5′,6 | 0.8 | 0.11 | 0.12 | 0.02 | 0.02 |
| Total | | | 4.09 | 6.48 | 0.65 | 1.12 |
| Total PCBs | | | 7.47 | 10.71 | 1.19 | 1.75 |

[a]Elute before DDE.
[b]Markers for occupational exposure.
[c]Elute after DDE.

**Table 2b.** Current serum PCB concentrations in women who participated in the study ($N = 112$).

| IUPAC number | IUPAC structure | % of non-detectable or zero values | Wet weight (ng/g) | | Lipid basis ($\mu$g/g) | |
|---|---|---|---|---|---|---|
| | | | Geometric mean | SD | Geometric mean | SD |
| *Light PCBs*[a] | | | | | | |
| PCB-28[b] | 2,4,4′ | 15.2 | 0.11 | 1.53 | 0.02 | 0.27 |
| PCB-74[b] | 2,4,4′,5 | 6.3 | 0.55 | 6.25 | 0.08 | 1.24 |
| PCB-66 | 2,3′,4,4′ | 10.7 | 0.21 | 0.34 | 0.03 | 0.06 |
| PCB-56 | 2,3,3′,4′ | 15.2 | 0.09 | 0.26 | 0.01 | 0.05 |
| PCB-101 | 2,2′,4,5,5′ | 6.3 | 0.26 | 0.30 | 0.04 | 0.05 |
| PCB-99 | 2,2′,4,4′,5 | 5.4 | 0.15 | 0.46 | 0.02 | 0.09 |
| Total | | | 2.29 | 7.99 | 0.34 | 1.57 |
| *Heavy PCBs*[c] | | | | | | |
| PCB-118[b] | 2,3′,4,4′,5 | 4.5 | 0.23 | 1.08 | 0.03 | 0.21 |
| PCB-146 | 2,2′,3,4′,5,5′ | 6.3 | 0.05 | 0.33 | 0.01 | 0.07 |
| PCB-153 | 2,2′,4,4′,5,5′ | 1.8 | 0.71 | 1.94 | 0.10 | 0.39 |
| PCB-105[b] | 2,3,3′,4,4′ | 8.9 | 0.05 | 0.21 | 0.01 | 0.04 |
| PCB-138 | 2,2′,3,4,4′,5′ | 1.8 | 0.54 | 2.40 | 0.08 | 0.49 |
| PCB-178 | 2,2′,3,3′,5,5′,6 | 9.8 | 0.03 | 0.08 | 0.004 | 0.01 |
| PCB-187 | 2,2′,3,4′,5,5′,6 | 1.8 | 0.12 | 0.21 | 0.02 | 0.04 |
| PCB-183 | 2,2′,3,4,4′,5′,6 | 2.7 | 0.05 | 0.06 | 0.01 | 0.01 |
| PCB-167 | 2,3′,4,4′,5,5′ | 15.2 | 0.03 | 0.14 | 0.004 | 0.03 |
| PCB-174 | 2,2′,3,3′,4,5,6′ | 2.7 | 0.06 | 0.04 | 0.01 | 0.01 |
| PCB-177 | 2,2′,3,3′,4,5′,6′ | 9.8 | 0.04 | 0.08 | 0.01 | 0.02 |
| PCB-156[b] | 2,3,3′,4,4′,5 | 9.8 | 0.11 | 0.89 | 0.02 | 0.17 |
| PCB-172 | 2,2′,3,3′,4,5,5′ | 11.6 | 0.05 | 0.09 | 0.01 | 0.02 |
| PCB-180 | 2,2′,3,4,4′,5,5′ | 0.9 | 0.38 | 0.84 | 0.06 | 0.16 |
| PCB-170 | 2,2′,3,3′,4,4′,5 | 0.9 | 0.16 | 0.51 | 0.02 | 0.10 |
| PCB-199 | 2,2′,3,3′,4,5,5′,6′ | 0.0 | 0.08 | 0.12 | 0.01 | 0.02 |
| PCB-203 | 2,2′,3,4,4′,5,5′,6 | 0.9 | 0.07 | 0.08 | 0.01 | 0.02 |
| Total | | | 3.21 | 8.58 | 0.47 | 1.72 |
| Total PCBs | | | 5.81 | 15.63 | 0.86 | 3.11 |

[a]Elute before DDE.
[b]Markers for occupational exposure.
[c]Elute after DDE.

($\beta = 0.176$, $P \leq 0.001$) and among persons with less education ($\beta = -0.022$, $P = 0.041$). BMI was positively associated with log current serum PCB concentrations, but this association was statistically significant only for the light congeners ($\beta = 0.012$, $P = 0.032$).

Table 3 demonstrates that reported total cumulative occupational exposure to PCBs was significantly and positively associated with log 2004 serum total PCB concentration ($\beta = 0.056$, $P \leq 0.001$) after adjustment for age, gender, education, and BMI. This association was strongest for the occupational light congeners, especially PCB-74 ($R^2 = 0.16$), although some heavy congeners, such as PCB-105 and 156, were also statistically significant. In general, the associations for heavy congeners present in the Aroclor mixtures used by workers were weaker in magnitude than those for the light congeners, and less difference was observed between the occupational and non-occupational heavy congeners compared with the lighter congeners.

Cumulative exposure during the years that Aroclor 1016 was used was most strongly related to the occupational light congeners, particularly PCB-74 ($\beta = 0.249$, $P \leq 0.001$, $R^2 = 0.17$), although two heavy occupational congeners (PCB-105 and 118) were also significant. In contrast, the strength of the association between log serum PCB levels and cumulative occupational exposure during the years that Aroclor 1242 was used was similar for both the occupational light ($\beta = 0.056$, $P \leq 0.001$, $R^2 = 0.09$) and occupational heavy congeners ($\beta = 0.032$, $P \leq 0.001$, $R^2 = 0.07$). Occupational exposure to Aroclor 1254 was significantly associated with only one congener (PCB-156).

Only seven participants (3%) ever ate fish from the Hudson River, and only two persons (1%) ate fish from the Hudson River after 1994 (data not shown). Thirty

**Table 3.** Multiple regression analysis of current serum PCB concentration (log adjusted, lipid basis) on Aroclor mixture use during years when participants were occupationally exposed[a] (log adjusted), by congener ($N = 233$).

| Congener | Aroclor mixture in use during years when occupationally exposed | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Aroclor 1254 (years of use: 1946–1953) | | Aroclor 1242 (years of use: 1954–1972) | | Aroclor 1016 (years of use: 1973–1977) | | Total (years of use: 1946–1977) | |
| | $\beta^b$ | $R^2$ | $\beta^b$ | $R^2$ | $\beta^b$ | $R^2$ | $\beta^b$ | $R^2$ |
| Light PCBs[c] | −0.014 | 0.03 | 0.044*** | 0.10 | 0.041*** | 0.07 | 0.082*** | 0.09 |
| Occupational light PCBs | −0.016 | 0.00 | 0.056*** | 0.09 | 0.078*** | 0.15 | 0.144*** | 0.15 |
| PCB-28 | 0.005 | 0.00 | 0.083 | 0.01 | 0.063 | 0.01 | 0.104 | 0.00 |
| PCB-74 | −0.053 | 0.00 | 0.146*** | 0.07 | 0.249*** | 0.17 | 0.432*** | 0.16 |
| Non-Occupational light PCBs | 0.015 | 0.00 | 0.054* | 0.03 | 0.002 | 0.00 | 0.040 | 0.00 |
| Heavy PCBs[d] | 0.018 | 0.00 | 0.022*** | 0.06 | 0.012 | 0.02 | 0.037** | 0.05 |
| Occupational heavy PCBs | 0.021 | 0.00 | 0.032*** | 0.07 | 0.027** | 0.04 | 0.060*** | 0.06 |
| PCB-105 | −0.093 | 0.00 | 0.151** | 0.05 | 0.152** | 0.04 | 0.278** | 0.04 |
| PCB-118 | −0.122 | 0.00 | 0.100** | 0.04 | 0.085* | 0.02 | 0.112 | 0.01 |
| PCB-156 | 0.177* | 0.02 | 0.048 | 0.02 | 0.019 | 0.00 | 0.126* | 0.03 |
| Non-occupational heavy PCBs | 0.045 | 0.00 | 0.043*** | 0.05 | 0.019 | 0.01 | 0.071** | 0.03 |
| Total PCBs | 0.009 | 0.00 | 0.030*** | 0.08 | 0.023** | 0.04 | 0.056*** | 0.08 |

[a]Cumulative occupational exposure based on industrial hygienist assessment and years on job; partitioned according to years when each Aroclor mixture was used.
[b]Adjusted for age, gender, education, and BMI.
[c]Elute before DDE: PCB-28, PCB-74, PCB-66, PCB-56, PCB-101, PCB-99.
[d]Elute after DDE: PCB-118, PCB-146, PCB-153, PCB-105, PCB-138, PCB-178, PCB-187, PCB-183, PCB-167, PCB-174, PCB-177, PCB-156, PCB-172, PCB-180, PCB-170, PCB-201, PCB-203.
*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$.

individuals (13%) reported consuming fish from Lakes Ontario or Champlain, and 85 persons (36%) ate fish from other fresh bodies of water in New York. Combining these data yielded a total of 92 persons who ate a median of 47 fresh water fish meals in their lifetime. In contrast to occupational exposure, there were no significant differences in serum concentrations by total cumulative fresh water fish consumption for total PCB, light or heavy PCBs, or for individual congeners (data not shown).

### *Current* versus *Archived Serum PCB Concentrations*

The geometric means of the archived and current serum PCB values, expressed on a wet weight basis, for the five occupational congeners, their light, heavy, and total sums, and the light, heavy, and total PCB values are shown in Table 4, separately for men and women and combined by gender for the 45 study participants with both measurements. Serum total PCB concentrations for men and women combined decreased significantly from a geometric mean of 37.8 ng/g in 1976 to 9.8 ng/g currently ($P \leq 0.001$). The relative decline was greater for the occupational light congeners (geometric mean of 21.3 ng/g to 2.8 ng/g) than for the occupational heavy congeners (geometric mean of 2.7 ng/g to 0.9 ng/g). Current serum PCB concentrations were significantly higher in women than men for congeners of both occupational origin and light, heavy, and total PCBs. Graphs of the relationships of serum PCB concentrations (log transformed) between archived and current samples for light, heavy, and total PCBs are presented in Figures 1a, 1b and 1c, respectively, separated into men and women after the removal of one extreme value for women. These results continue to indicate a strong association between values for the two time points, and that this association was greater for light congeners and for total PCB among women than men.

### *Half-Life Estimates*

The half-lives of the occupational PCB congeners are shown in Table 5. They ranged from 4.6 years for PCB-28 to 41.0 years for PCB-156 when the data for men and women were combined. The half-life for the heavy congeners (17.8 years) was approximately twice that for the light PCBs (9.6 years). There were also gender differences with women exhibiting half-lives ranging from 1.5 to 10 times longer than those seen in men.

Table 6 shows the half-lives of the occupational PCB congeners according to whether the 1976 concentrations were above or below (''high'' or ''low'', respectively) the median serum PCB values for each group. These data indicate that PCB half-lives are greater among the low exposure group than in the high exposure group, with half-lives varying by a factor of 2 to 10. In addition, this inverse association between initial exposure levels and half-life estimates tended to be stronger for the heavy compared with light congeners.

## Discussion

Of the 241 persons in the recreated cohort, a subgroup of 45 had serum PCB levels determined from both 1976 and

**Table 4.** Geometric means of current PCB concentrations (wet weight, ng/g) in sera from archived cohort ($N = 45$) for men, women, and all (men and women combined) capacitor workers[a].

| PCB Congener or summed score | 1976 Men and women combined | 2004 Men and women combined | 1976 Men | 2004 Men | 1976 Women | 2004 Women |
|---|---|---|---|---|---|---|
| *Occupational PCBs*[b] | | | | | | |
| PCB-28 | 11.27 | 0.17** | 12.13 | 0.11* | 9.23 | 0.49* |
| PCB-74 | 7.75 | 2.29*** | 8.67 | 1.74*** | 5.71 | 4.89 + |
| PCB-105 | 0.58 | 0.14** | 0.68 | 0.12*** | 0.36 | 0.24 |
| PCB-118 | 1.71 | 0.42*** | 1.69 | 0.32*** | 1.77 | 0.91 + |
| PCB-156 | 0.21 | 0.23 | 0.24 | 0.21** | 0.15 | 0.30 |
| *Occupational summed PCBs* | | | | | | |
| Occupational light[b] | 21.27 | 2.80*** | 23.20 | 2.15** | 16.77 | 5.79* + |
| Occupational heavy[b] | 2.74 | 0.92** | 2.78 | 0.76*** | 2.62 | 1.55 + |
| Occupational total[b] | 24.56 | 3.86*** | 26.56 | 3.05*** | 19.80 | 7.44* + |
| *Summed PCBs*[c] | | | | | | |
| Light PCBs | 26.41 | 4.28*** | 28.82 | 3.58** | 20.76 | 6.98* + |
| Heavy PCBs | 9.08 | 5.05** | 9.01 | 4.42*** | 9.27 | 7.29 + |
| Total PCBs | 37.82 | 9.80*** | 40.37 | 8.38*** | 31.62 | 15.05* + |

[a]Total $N = 45$ (33 men and 12 women) in 1976 and in 2004.
[b]Occupational light = PCB28 + PCB74. Occupational heavy = PCB105 + PCB118 + PCB156. Occupational total = occupational light + occupational heavy.
[c]Summed PCBs are the sum of all occupational (PCB congener numbers 28, 74, 105, 118, and 156) and non-occupational (PCB congener numbers 66, 56, 101, 99, 146, 138, 178, 187, 183, 167, 174, 177, 153, 172, 180, 170, 201, and 203) PCB congeners.
*$P \leq 0.05$, paired $t$-test significant comparing 1976 and 2004 PCB concentrations.
**$P \leq 0.01$, paired $t$-test significant comparing 1976 and 2004 PCB concentrations.
***$P \leq 0.001$, paired $t$-test significant comparing 1976 and 2004 PCB concentrations.
+ $P \leq 0.05$, $t$-test significant comparing 2004 PCB concentrations for male vs female.

2004. A 75% decline in geometric mean serum total PCB concentration was observed in this subgroup over the 28-year period. This decrease was proportionately greater for the congeners thought to be of occupational origin than for all congeners combined and for the light congeners compared with the heavy congeners. Interestingly, the current serum concentrations for women were approximately twice those of the men, although their 1976 levels were lower than those for men.

Our serum PCB half-life estimates reflect these findings. For example, the half-life for all the occupational congeners combined was approximately 10 years, yielding about three half-lives over the study period. Similarly, shorter half-lives were found for the occupational light congeners, whereas the half-life for serum PCB concentrations in men was only 50% that of women. This difference in half-lives by sex may also explain why the association between the 1976 and 2004 serum concentrations was greater among women compared with men, at least for the light congeners. We also found an inverse relationship between initial serum levels and half-lives, with those workers whose 1976 concentrations were below the median having a half-life approximately twice that of those whose 1976 concentrations were above the median. As men had higher serum PCB levels in 1976 than did women, this difference in half-lives, according to initial serum PCB concentrations, may explain the greater half-lives for all categories of PCB congeners in women compared with men. Differences in BMI by gender probably are not involved, given the fact that BMI was not associated with half-life.

Similar associations were reported by Wolff et al. (1992), although their half-life estimates were shorter for the light, compared with heavy congeners, and for those individuals with high compared with those individuals with lower initial exposure. For the most part, however, the individual half-lives of the PCB congeners determined in this study are significantly longer than those reported by Wolff et al. (1992) with the exception of PCB-28. These differences in estimated half-lives between the two studies most likely reflect the longer time period over which we were able to estimate half-lives. Indeed, it has been shown that serum PCB concentrations decay in a non-linear, at least two-component, pharmacokinetic manner with the greatest decreases occurring shortly after exposure (Yakushiji et al., 1984; Lawton et al., 1985; Phillips et al., 1989b). Thus, for the PCB congeners with long half-lives, the half-lives estimated over the shorter interval (3.8 years) used by Wolff and co-workers would have emphasized this earlier and more rapid decline in serum PCBs, and therefore may be responsible for their shorter estimates of half-lives. Furthermore, due to the relatively short interval between the initial and follow-up

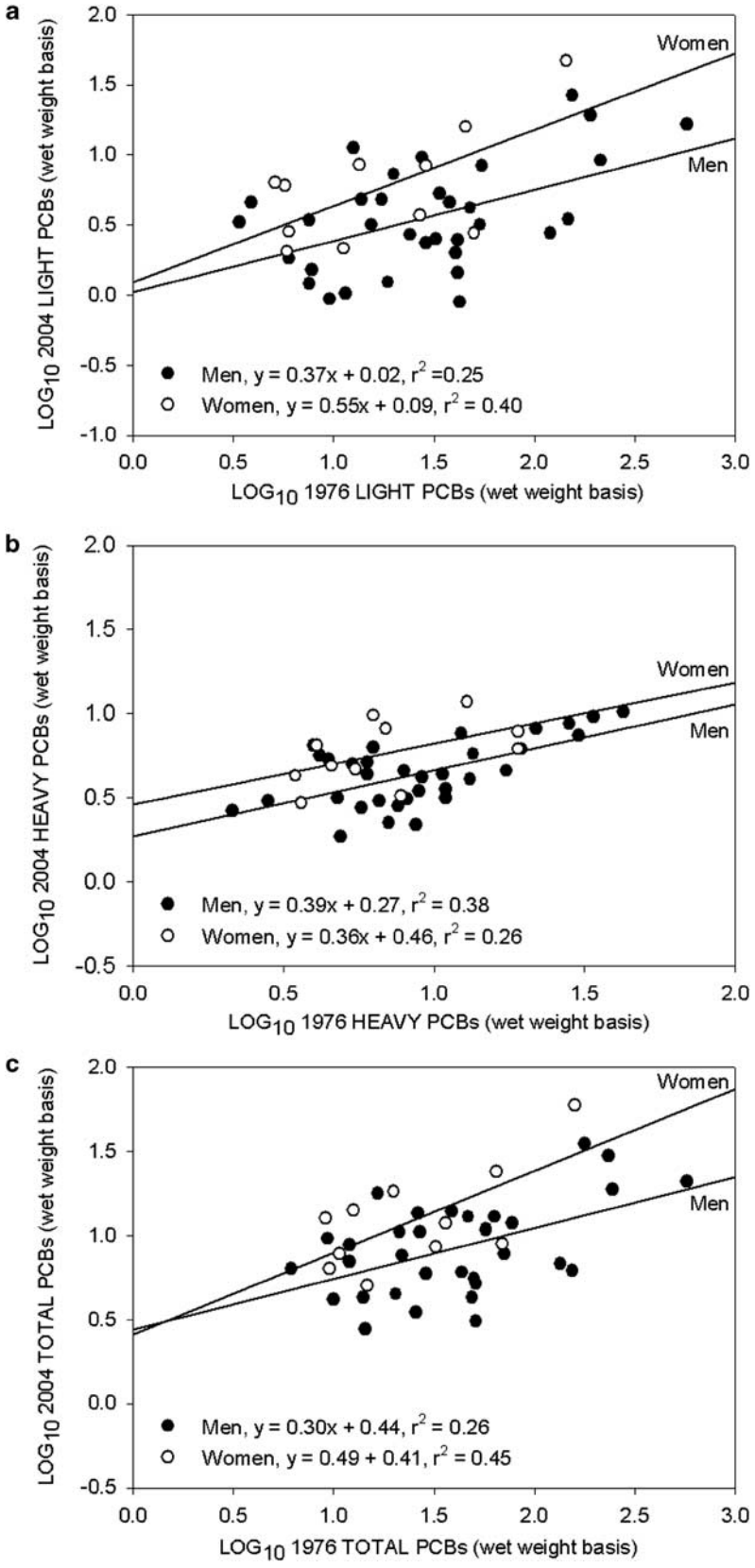


**Figure 1.** Graphs of the 1976–2004 relationships for log-transformed light (**a**), heavy (**b**), and total (**c**) PCBs expressed on a wet weight basis (ng/g) in men and women from the archived cohort ($N = 45$).

serum PCB measures available to Wolff and co-workers, two of the congeners reported to have an infinite half-life (PCB-74, 156) have now been estimated to have half-lives of 15.9 and 41 years, respectively.

Regarding the serum concentrations of the 241-person cohort as a whole, their geometric mean 2004 level for total serum PCB concentration of 6.65 ng/g (wet weight) or 1.02 μg/g (lipid weight) is approximately twofold higher than that for similarly aged individuals who resided in the same towns at that time, but did not work at GE (Fitzgerald et al., 2007a). This finding, that PCB levels remain elevated more than 30 years after the last direct occupational exposure to PCBs, confirms not only the high levels of occupational exposure but also our estimates of long half-lives for many congeners. Lightly chlorinated congeners, especially those thought to be occupational in origin (PCB-28, 74), were more dominant in the serum of capacitor workers than in the serum of individuals from the general population in the same towns (Fitzgerald et al., 2007a). This finding most likely reflects the impact of occupational exposure to Aroclor 1016 and 1242 in the later years during which PCBs were used.

The continuing impact of previous occupation also was apparent when regression analyses revealed that the 2004 serum PCB concentrations were positively and significantly associated with cumulative years of occupational exposure. In addition, these associations tended to be stronger for the occupational congeners (PCB-74, 105, 118, and 156) than for the non-occupational congeners. Furthermore, the associations with the occupational light congeners were strongest for exposures during the years when Aroclor 1016 was used. Associations between serum concentrations of light and heavy occupational congeners and exposure to Aroclor 1242 were similar. These findings reflect the fact that Aroclor 1016 is composed of lightly chlorinated congeners, whereas Aroclor 1242 is a mixture of both light and heavy congeners (Erickson, 1997). The magnitude of the association, however, was relatively modest, with a maximum $R^2$ of 17% for

**Table 5.** PCB half-lives in years (calculated using the geometric means of data expressed on a wet weight basis) for capacitor workers from archived cohort ($N = 45$)[a].

| PCB Congener or summed score | Half-life men and women combined | Half-life men | Half-life women |
|---|---|---|---|
| *Occupational PCBs* | | | |
| PCB-28 | 4.6 | 4.2 | 6.6** |
| PCB-74 | 15.9 | 12.1 | 124.9* |
| PCB-105 | 13.7 | 10.9 | 46.5 |
| PCB-118 | 13.8 | 11.6 | 29.2** |
| PCB-156 | 41.0 | 33.3 | 90.1 |
| *Occupational summed PCBs* | | | |
| Occupational light[b] | 9.6 | 8.2 | 18.2** |
| Occupational heavy[b] | 17.8 | 14.9 | 37.2* |
| Occupational total[b] | 10.5 | 9.0 | 19.8** |

[a]Total $N = 45$ (33 men and 12 women) in 1976 and in 2004.
[b]Occupational light = PCB28 + PCB74. Occupational heavy = PCB105 + PCB118 + PCB156. Occupational Total = occupational light + occupational heavy.
*$P \leq 0.05$, significant rank transformation analysis of variance test between men and women.
**$P \leq 0.01$, significant rank transformation analysis of variance test between men and women.

**Table 6.** Geometric means of archived and current concentrations (ng/g wet weight) and calculated half-lives for high and low 1976 total PCB exposure groups from archived cohort ($N = 45$)[a].

| PCB congener or summed score | Geometric mean | | | Geometric mean | | |
|---|---|---|---|---|---|---|
| | 1976 Low | 2004 Low | Half-life low | 1976 High | 2004 High | Half-life high |
| *Occupational PCBs* | | | | | | |
| PCB-28 | 4.62 | 0.20 | 6.13 | 28.65 | 0.14 | 3.67*** |
| PCB-74 | 2.94 | 1.47 | 28.10 | 21.36 | 3.63 | 10.95* |
| PCB-105 | 0.23 | 0.09 | 19.92 | 1.49 | 0.23 | 10.35*** |
| PCB-118 | 0.76 | 0.30 | 21.28 | 4.00 | 0.59 | 10.10*** |
| PCB-156 | 1.03 | 0.94 | 214.80 | 2.65 | 1.17 | 23.71 |
| *Occupational summed PCBs* | | | | | | |
| Occupational light[b] | 8.13 | 1.94 | 13.56 | 58.16 | 4.11 | 7.32** |
| Occupational heavy[b] | 1.26 | 0.70 | 32.65 | 6.14 | 1.22 | 12.01*** |
| Occupational total[b] | 9.47 | 2.71 | 15.52 | 66.49 | 5.59 | 7.84*** |

[a]Total $N = 45$ (33 men and 12 women) in 1976 and in 2004; $N = 23$, low exposure (1976 TPCBs $\leq 36.534$ (median)) and $N = 22$ and high exposure (1976 TPCBs $> 36.534$ (median)).
[b]Occupational light = PCB28 + PCB74. Occupational heavy = PCB105 + PCB118 + PCB156. Occupational total = occupational light + occupational heavy.
*$P \leq 0.05$, significant rank transformation analysis of variance test between high and low exposure groups for half-lives.
**$P \leq 0.01$, significant rank transformation analysis of variance test between high and low exposure groups for half-lives.
***$P \leq 0.001$, significant rank transformation analysis of variance test between high and low exposure groups for half-lives.

PCB-74 and occupational exposure during the years that Aroclor 1016 was used, probably due to the fact that nearly 30 years has elapsed from the time of last exposure. Only one congener was significantly associated with Aroclor 1254, which is likely related to the observation that only 10% of the study population was employed during the years that Aroclor 1254 was used. Employment during the years that Aroclor 1254 was used was moderately correlated with Aroclor 1242 ($r = 0.56$), but not associated with Aroclor 1016 ($r = -0.01$). In contrast, serum PCB concentrations were not associated with reported consumption of fish from PCB-contaminated bodies of fresh water in New York State, suggesting that the major source of PCB exposure in this cohort indeed was occupational.

Examination of the relationships between 2004 serum PCB concentrations and demographic variables provides additional insights, as well as confirming that the results reported here are similar to those found in previous studies. Current serum PCB concentrations were significantly and positively associated with the age of the individual, a finding that has been previously reported (Wolff et al., 2005). There were also significant gender differences in current serum lipid-adjusted PCB concentrations, with men in our cohort having higher serum PCB concentrations than women. This finding was not unexpected as men were more likely than women to have been occupationally exposed to PCBs, and thus had higher initial serum PCB levels. In addition, there were significant negative associations between both occupational light and total PCB concentrations and the number of years of education reported by the former capacitor plant workers. These associations most likely reflect the types of jobs held by the individuals, as $\sim$85% of those with a high school education or less were occupationally exposed compared with $\sim$74% of those who had some college education. Finally, BMI was positively associated with an increase in serum concentrations of lightly chlorinated PCBs. The findings of other studies, with regard to BMI are, however, mixed with some investigators reporting positive correlations (Falk et al., 1999; Fitzgerald et al., 2007a), whereas others have found either inverse associations (Wolff et al., 2000) or none (Hanrahan et al., 1999). For a review, the issues surrounding associations with BMI, see Wolff et al. (2005, 2007).

The major strength of this study is the ability to compare serum PCB concentrations in the same group of highly exposed persons over nearly three decades. With this information, we were able to more accurately and completely estimate half-lives for many congeners than was possible with shorter periods of follow-up. The fact that the PCB determinations were made by the same laboratory at the same time using the same analytical methods facilitated this comparison.

As in all observational studies, however, our findings should be considered in the context of possible limitations. For example, one possible problem is selection bias that might alter the type of persons participating in the study and their health status. Our results showed that, while the gender composition of the final study population ($N = 241$) did not differ from that of the source population, this group did differ in terms of both age and probable occupational PCB exposure level. The younger mean age of the participants probably reflects the fact that older persons were more likely to have died before the tracing began. The finding that the study participants were more likely to have been heavily exposed according to the original job codes reflected the fact that exposure levels were among the criteria used to select participants for recruitment in this study, that is, persons in the high exposure group were oversampled. As current serum PCB concentrations were measured prospectively, however, systematic bias is unlikely. In general, the 45-person subgroup that had both current and historical serum PCB data was similar to the larger cohort of 241 individuals. The only exceptions were among women, with those in the 45 person subgroup being older, more likely to have had children, and of lower BMI. These factors, however, should not bias the half-life data, as they were based on intra-person comparisons, and age, parity, and BMI were not associated with our estimates of half-lives.

An additional limitation that restricted our ability to better define the PCB half-lives was the relatively small sample size of those individuals for whom we had archived sera values, the 45-person subgroup, especially as it included only 12 women. A larger sample size would have allowed us to stratify both men and women into ''high'' and ''low'' exposures in order to determine whether the recognized inverse relationship between initial serum PCB concentrations and half-lives differed between men and women. Another limitation is the relatively crude nature of the exposure assessment for fish consumption, which did not take into account the PCB concentration(s) of any fish consumed. Hence, it is possible that some non-differential misclassification may have been introduced, making it more difficult to detect an association between serum PCB concentrations and fish consumption. We also did not have individual determinations of PCB intake from fish or other foodstuffs, restricting our half-life estimates to those five congeners that were primarily of occupational origin.

## Conclusion

In summary, serum PCB concentrations in this cohort of former capacitor plant workers, determined nearly 30 years after direct occupational exposures ceased, remained substantially elevated relative to serum PCB levels seen in individuals residing in the same communities who did not work at the GE capacitor factories. By comparing serum concentrations in a subgroup of workers from 1976 to 2004, we demonstrated that some of the congeners that were

occupational in origin have longer half-lives than previously estimated. In general, the half-lives for light occupational congeners were shorter than those for heavy congeners. We have also shown that half-lives for the occupational congeners were inversely proportional to initial body burdens that may aid in explaining the significantly longer half-lives we observed in women. The revised half-lives should further aid in understanding the toxicological/epidemiological consequences of exposure to PCBs, as well as identifying earlier vectors of exposure to PCBs. Finally, earlier occupational exposure remained a significant predictor of current serum PCB concentrations, further supporting a consistent and long-duration trend of increased PCB body burden in this cohort of former capacitor workers.

## Conflict of interest

The authors declare no conflict of interest.

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